WEST

Freeform Search

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Term: L4 and (nucleic acid or polynucleotide or DNA)

Display: 10 **Documents in Display Format:** CIT **Starting with Number** 1

Generate: ○ Hit List ◉ Hit Count ○ Image

Search | Clear | Help | Logout | Interrupt

Main Menu | Show S Numbers | Edit S Numbers | Preferences

Search History

Today's Date: 1/17/2002

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	L4 and (nucleic acid or polynucleotide or DNA)	25	L5
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	CPT-11 and (CE or carboxylesterase)	28	L4
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l2 and glucocoticoid$	0	L3
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	human near myoblast$	51	L2
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	human near muscle cell line	3	L1

$%^STN;HighlightOn= ***;HighlightOff=*** ;
Trying 3106016892...Open

Welcome to STN International! Enter x:x
LOGINID:ssspta1633cxq
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

********** Welcome to STN International **********

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 Sep 17 IMSworld Pharmaceutical Company Directory name change to PHARMASEARCH
NEWS 3 Oct 09 Korean abstracts now included in Derwent World Patents Index
NEWS 4 Oct 09 Number of Derwent World Patents Index updates increased
NEWS 5 Oct 15 Calculated properties now in the REGISTRY/ZREGISTRY File
NEWS 6 Oct 22 Over 1 million reactions added to CASREACT
NEWS 7 Oct 22 DGENE GETSIM has been improved
NEWS 8 Oct 29 AAASD no longer available
NEWS 9 Nov 19 New Search Capabilities USPATFULL and USPAT2
NEWS 10 Nov 19 TOXCENTER(SM) - new toxicology file now available on STN
NEWS 11 Nov 29 COPPERLIT now available on STN
NEWS 12 Nov 29 DWPI revisions to NTIS and US Provisional Numbers
NEWS 13 Nov 30 Files VETU and VETB to have open access
NEWS 14 Dec 10 WPINDEX/WPIDS/WPIX New and Revised Manual Codes for 2002
NEWS 15 Dec 10 DGENE BLAST Homology Search
NEWS 16 Dec 17 WELDASEARCH now available on STN
NEWS 17 Dec 17 STANDARDS now available on STN
NEWS 18 Dec 17 New fields for DPCI
NEWS 19 Dec 19 CAS Roles modified
NEWS 20 Dec 19 1907-1946 data and page images added to CA and CAplus

NEWS EXPRESS August 15 CURRENT WINDOWS VERSION IS V6.0c, CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP), AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

********** STN Columbus **********

FILE 'HOME' ENTERED AT 12:53:58 ON 17 JAN 2002

=> FIL EMBASE BIOSIS CAPLUS
COST IN U.S. DOLLARS SINCE FILE TOTAL
ENTRY SESSION
FULL ESTIMATED COST 2.85 2.85

FILE 'EMBASE' ENTERED AT 13:05:27 ON 17 JAN 2002
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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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=> FIL REGISTRY
COST IN U.S. DOLLARS SINCE FILE TOTAL
ENTRY SESSION
FULL ESTIMATED COST 8.62 11.47

FILE 'REGISTRY' ENTERED AT 13:12:48 ON 17 JAN 2002
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STRUCTURE FILE UPDATES: 15 JAN 2002 HIGHEST RN 383362-48-9
DICTIONARY FILE UPDATES: 15 JAN 2002 HIGHEST RN 383362-48-9

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s irinotecan
L1 4 IRINOTECAN

=> d bib abs 1-
'BIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'
'ABS' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual fields or predefined formats. The predefined substance formats are: (RN = CAS Registry Number)

REG - RN
SAM - Index Name, MF, and structure - no RN
FIDE - All substance data, except sequence data
IDE - FIDE, but only 50 names
SQIDE - IDE, plus sequence data
SQIDE3 - Same as SQIDE, but 3-letter amino acid codes are used
SQD - Protein sequence data, includes RN
SQD3 - Same as SQD, but 3-letter amino acid codes are used
SQN - Protein sequence name information, includes RN

CALC - Table of numeric properties
PROP - Same as CALC

ABS -- Abstract
APPS -- Application and Priority Information
BIB -- CA Accession Number, plus Bibliographic Data
CAN -- CA Accession Number
CBIB -- CA Accession Number, plus Bibliographic Data (compressed)
IND -- Index Data
IPC -- International Patent Classification
PATS -- PI, SO
STD -- BIB, IPC, and NCL

IABS --ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.
The MAX format is the same as ALL.
The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

ENTER DISPLAY FORMAT (IDE):
ENTER DISPLAY FORMAT (IDE):bib
'BIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

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HELP FORMATS -- To see detailed descriptions of the predefined formats.
Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

ENTER DISPLAY FORMAT (IDE):abs
'ABS' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual fields or predefined formats. The predefined substance formats are: (RN = CAS Registry Number)

REG - RN
SAM - Index Name, MF, and structure - no RN
FIDE - All substance data, except sequence data
IDE - FIDE, but only 50 names
SQIDE - IDE, plus sequence data
SQIDE3 - Same as SQIDE, but 3-letter amino acid codes are used
SQD - Protein sequence data, includes RN
SQD3 - Same as SQD, but 3-letter amino acid codes are used
SQN - Protein sequence name information, includes RN

CALC - Table of numeric properties
PROP - Same as CALC

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IABS --ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.
The MAX format is the same as ALL.
The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

ENTER DISPLAY FORMAT (IDE):IDE
Connection closed by remote host

<------User Break------>
Trying 3106016892...Open

Welcome to STN International! Enter x:x
LOGINID:ssspta1633cxq
PASSWORD:jun13cxq
* * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'REGISTRY' AT 13:17:06 ON 17 JAN 2002
FILE 'REGISTRY' ENTERED AT 13:17:06 ON 17 JAN 2002
COPYRIGHT (C) 2002 American Chemical Society (ACS)
ENTER DISPLAY FORMAT (IDE):

---Logging off of STN---

ENTER DISPLAY FORMAT (IDE):END

=>
Executing the logoff script...

=> LOG Y
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 5.60 17.07

STN INTERNATIONAL LOGOFF AT 13:17:37 ON 17 JAN 2002

Trying 3106016892...Open

Welcome to STN International! Enter x:x
LOGINID:ssspta1633cxq
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

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NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:18:00 ON 17 JAN 2002

=> FIL REGISTRY
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 0.15 0.15

FILE 'REGISTRY' ENTERED AT 13:18:08 ON 17 JAN 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 15 JAN 2002 HIGHEST RN 383362-48-9
DICTIONARY FILE UPDATES: 15 JAN 2002 HIGHEST RN 383362-48-9

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES
for more information. See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> s irinotecan
L1 4 IRINOTECAN

=> d bib abs
'BIB' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'
'ABS' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

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CALC - Table of numeric properties
PROP - Same as CALC

ABS -- Abstract
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OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when
it is available.
The MAX format is the same as ALL.
The IALL format is the same as ALL with BIB ABS and IND indented,
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For additional information, please consult the following help
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HELP FORMATS -- To see detailed descriptions of the predefined formats.
Any CA File format may be combined with any substance format to
obtain CA references citing the substance. The substance formats
must be cited first. The CA File predefined formats are:

ENTER DISPLAY FORMAT (IDE):SAM

L1 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2002 ACS
IN ***DNA (rabbit carboxyl esterase Irinotecan-activating cDNA plus flanks)***
*** (9CI)***
SQL 1717
MF Unspecified
CI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***

=> d IND
'IND' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual
fields or predefined formats. The predefined substance formats
are: (RN = CAS Registry Number)

REG - RN
SAM - Index Name, MF, and structure - no RN
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SQD - Protein sequence data, includes RN
SQD3 - Same as SQD, but 3-letter amino acid codes are used
SQN - Protein sequence name information, includes RN

CALC - Table of numeric properties
PROP - Same as CALC

ABS -- Abstract
APPS -- Application and Priority Information
BIB -- CA Accession Number, plus Bibliographic Data
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ISTD -- STD format, indented

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when
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HELP FORMATS -- To see detailed descriptions of the predefined formats.
Any CA File format may be combined with any substance format to
obtain CA references citing the substance. The substance formats
must be cited first. The CA File predefined formats are:

ENTER DISPLAY FORMAT (IDE):IDE

L1 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2002 ACS
RN 209370-55-8 REGISTRY
CN ***DNA (rabbit carboxyl esterase Irinotecan-activating cDNA plus flanks)***
*** (9CI)*** (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF036930
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: CA, CAPLUS, GENBANK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> d STD 1-
'STD' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual
fields or predefined formats. The predefined substance formats
are: (RN = CAS Registry Number)

REG - RN
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SQIDE3 - Same as SQIDE, but 3-letter amino acid codes are used

SQD - Protein sequence data, includes RN
SQD3 - Same as SQD, but 3-letter amino acid codes are used
SQN - Protein sequence name information, includes RN

CALC - Table of numeric properties
PROP - Same as CALC

ABS -- Abstract
APPS -- Application and Priority Information
BIB -- CA Accession Number, plus Bibliographic Data
CAN -- CA Accession Number
CBIB -- CA Accession Number, plus Bibliographic Data (compressed)
IND -- Index Data
IPC -- International Patent Classification
PATS -- PI, SO
STD -- BIB, IPC, and NCL

IABS --ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.
The MAX format is the same as ALL.
The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

For additional information, please consult the following help messages:

HELP DFIELDS -- To see a complete list of individual display fields.
HELP FORMATS -- To see detailed descriptions of the predefined formats.
Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

ENTER DISPLAY FORMAT (IDE):IDE 1-
'1-' IS NOT A VALID FORMAT FOR FILE 'REGISTRY'

The following are valid formats:

Substance information can be displayed by requesting individual fields or predefined formats. The predefined substance formats are: (RN = CAS Registry Number)

REG - RN
SAM - Index Name, MF, and structure - no RN
FIDE - All substance data, except sequence data
IDE - FIDE, but only 50 names
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PROP - Same as CALC

ABS -- Abstract
APPS -- Application and Priority Information
BIB -- CA Accession Number, plus Bibliographic Data
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PATS -- PI, SO
STD -- BIB, IPC, and NCL

IABS --ABS, indented, with text labels
IBIB -- BIB, indented, with text labels
ISTD -- STD format, indented

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

The ALL format gives FIDE BIB ABS IND RE, plus sequence data when it is available.
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The IALL format is the same as ALL with BIB ABS and IND indented, with text labels.

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HELP FORMATS -- To see detailed descriptions of the predefined formats.
Any CA File format may be combined with any substance format to obtain CA references citing the substance. The substance formats must be cited first. The CA File predefined formats are:

ENTER DISPLAY FORMAT (IDE):IDE
YOU HAVE REQUESTED DATA FROM 4 ANSWERS - CONTINUE? Y/(N):y

L1 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2002 ACS
RN 209370-55-8 REGISTRY
CN ***DNA (rabbit carboxyl esterase Irinotecan-activating cDNA plus flanks)***
*** (9CI)*** (CA INDEX NAME)
OTHER NAMES:
CN GenBank AF036930
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR GenBank
LC STN Files: CA, CAPLUS, GENBANK

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L1 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2002 ACS
RN 203173-72-2 REGISTRY
CN [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4-ethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-11-(trimethylsilyl)-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN [1,4'-Bipiperidine]-1'-carboxylic acid, 4-ethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-11-(trimethylsilyl)-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, (S)-
OTHER NAMES:
CN ***(20S)-7-(Trimethylsilyl)irinotecan***
FS STEREOSEARCH
MF C34 H42 N4 O6 Si
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, TOXLIT, USPATFULL

Absolute stereochemistry. Rotation (+).

/ Structure 1 in file .gra /

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L1 ANSWER 3 OF 4 REGISTRY COPYRIGHT 2002 ACS
RN 100286-90-6 REGISTRY
CN [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline, [1,4'-bipiperidine]-1'-carboxylic acid deriv.
CN [1,4'-Bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride, (S)-
OTHER NAMES:
CN 7-Ethyl-10-[[4-(1-piperidyl)-1-piperidyl]carbonyloxy]camptothecin hydrochloride
CN Campto
CN Camptothecin 11
CN Camptothecin 11 hydrochloride
CN CPT 11
CN ***Irinotecan hydrochloride***
CN Topotecin
CN U 101440E
FS STEREOSEARCH
DR 111348-33-5
MF C33 H38 N4 O6 . Cl H
SR CA
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CHEMCATS, CIN, DDFU, DIOGENES,
DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR,
PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
CRN (97682-44-5)

Absolute stereochemistry. Rotation (+).

/ Structure 2 in file .gra /

/ Structure 3 in file .gra /

371 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
373 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L1 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2002 ACS
RN 97682-44-5 REGISTRY
CN [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline, [1,4'-bipiperidine]-1'-carboxylic acid deriv.
CN [1,4'-Bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, (S)-
OTHER NAMES:
CN ***(+)-Irinotecan***
CN Camptosar
CN ***Irinotecan***
FS STEREOSEARCH
MF C33 H38 N4 O6
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN,
CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, IPA, MRCK*,
PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).

/ Structure 4 in file .gra /

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

431 REFERENCES IN FILE CA (1967 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
435 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> CPT-11
CPT-11 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s CPT-11
54 CPT
739091 11
L2 1 CPT-11
(CPT(W)11)

=> d IDE

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 100286-90-6 REGISTRY
CN [1,4'-Bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1H-Pyrano[3',4':6,7]indolizino[1,2-b]quinoline, [1,4'-bipiperidine]-1'-carboxylic acid deriv.
CN [1,4'-Bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride, (S)-
OTHER NAMES:
CN 7-Ethyl-10-[[4-(1-piperidyl)-1-piperidyl]carbonyloxy]camptothecin hydrochloride
CN Campto
CN Camptothecin 11
CN Camptothecin 11 hydrochloride
CN ***CPT 11***
CN Irinotecan hydrochloride
CN Topotecin
CN U 101440E
FS STEREOSEARCH
DR 111348-33-5
MF C33 H38 N4 O6 . Cl H
SR CA
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
BIOBUSINESS, BIOSIS,
BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CHEMCATS, CIN, DDFU, DIOGENES,
DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR,
PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)
CRN (97682-44-5)

Absolute stereochemistry. Rotation (+).

/ Structure 5 in file .gra /

/ Structure 6 in file .gra /

371 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
373 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> d his

(FILE 'HOME' ENTERED AT 13:18:00 ON 17 JAN 2002)

FILE 'REGISTRY' ENTERED AT 13:18:08 ON 17 JAN 2002
L1 4 S IRINOTECAN
L2 1 S CPT-11

=> FIL EMBASE BIOSIS CAPLUS
COST IN U.S. DOLLARS SINCE FILE TOTAL
ENTRY SESSION
FULL ESTIMATED COST 25.46 25.61

FILE 'EMBASE' ENTERED AT 13:24:14 ON 17 JAN 2002

FILE 'BIOSIS' ENTERED AT 13:24:14 ON 17 JAN 2002

FILE 'CAPLUS' ENTERED AT 13:24:14 ON 17 JAN 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

=> s l2
L3 3200 L2

=> s l3 and (carboxylesterase or CE)
L4 133 L3 AND (CARBOXYLESTERASE OR CE)

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 83 DUP REM L4 (50 DUPLICATES REMOVED)

=> d bib abs 1-30

L5 ANSWER 1 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
AN 2001262762 EMBASE
TI A virus-directed enzyme prodrug therapy approach to purging neuroblastoma cells from hematopoietic cells using adenovirus encoding rabbit ***carboxylesterase*** and CPT-11.
AU Meck M.M.; Wierdl M.; Wagner L.M.; Burger R.A.; Guichard S.M.; Krull E.J.; Harris L.C.; Potter P.M.; Danks M.K.
CS M.K. Danks, Department of Molecular Pharmacology, St. Jude Children's Res. Hospital, 332 N. Lauderdale, Memphis, TN 38105, United States. mary.danks@stjude.org
SO Cancer Research, (1 Jul 2001) 61/13 (5083-5089).
Refs: 34
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
LA English
SL English
AB Tumor cells that contaminate hematopoietic cell preparations contribute to the relapse of neuroblastoma patients who receive autologous stem cell rescue as a component of therapy. Therefore, effective purging methods are needed. This study details in vitro experiments to develop a viral-directed enzyme prodrug purging method that specifically targets neuroblastoma cells. The approach uses an adenovirus to deliver the cDNA encoding a rabbit liver ***carboxylesterase*** that efficiently activates the prodrug irinotecan,7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11). The data show that an adenoviral multiplicity of infection of 50 transduces 100% of cultured neuroblastoma cells and primary tumor cells, irrespective of the level of tumor cell line contamination. Exposure of neuroblastoma cell lines or of mixtures of these cell lines with CD34(+) cells at a ratio of 10:90 to replication-deficient AdRSVrCE for 24 h and subsequent exposure of cells to 1-5 .mu.M CPT-11 for 4 h increased the toxicity of CPT-11 to three neuroblastoma cell lines (SJNB-1, NB-1691, and SK-N-SH) from .apprx.20-50-fold and eradicated their clonogenic potential. Also, after

"purging," RNA for neuroblastoma cell markers (tyrosine hydroxylase, synaptophysin, and N-MYC) was undetectable by reverse transcription-PCR. In contrast, the purging protocol did not affect the number or type of colonies formed by CD34(+) cells in an in vitro progenitor cell assay. No bystander effect on CD34(+) cells was observed. The method described is being investigated for its potential clinical utility, particularly its efficacy for use with patients having relatively high tumor burdens, because no published methods have been shown to be efficacious when the tumor burden exceeds 1%.

L5 ANSWER 2 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2
AN 2001262761 EMBASE
TI Sensitization of human tumor cells to CPT-11 via adenoviral-mediated delivery of a rabbit liver ***carboxylesterase*** .
AU Wierdl M.; Morton C.L.; Weeks J.K.; Danks M.K.; Harris L.C.; Potter P.M.
CS P.M. Potter, Department of Molecular Pharmacology, St. Jude Children's Res. Hospital, 332 N. Lauderdale, Memphis, TN 38105, United States. phil.potter@stjude.org
SO Cancer Research, (1 Jul 2001) 61/13 (5078-5082).
Refs: 26
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Irinotecan, 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) is activated by carboxylesterases (***CE***) to yield the potent topoisomerase I inhibitor, SN-38. We have demonstrated previously that a rabbit liver ***CE*** is approximately 100-1000-fold more efficient at drug activation than a highly homologous human ***CE*** . In an attempt to use rabbit ***CE*** expression in combination with CPT-11 for gene therapy approaches for the treatment of cancer, we have developed an adenoviral vector expressing this intracellular ***CE*** . After transduction, this virus produces very high levels of ***CE*** activity in a panel of human tumor cell lines and results in marked sensitization to CPT-11 of all of the transduced cells. Reductions in IC(50) values for this drug ranged from 11-127-fold. Additionally, comparison with an adenovirus expressing a secreted form of the rabbit ***CE*** indicated that a collateral effect could be achieved with reductions in the IC(50) values ranging from 4-19-fold. These data suggest that the described reagents may be suitable for use in vivo in a viral-directed enzyme prodrug therapy approach using CPT-11.

L5 ANSWER 3 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001379246 EMBASE
TI A new metabolite of irinotecan in which formation is mediated by human hepatic cytochrome P-450 3A4.
AU Sai K.; Kaniwa N.; Ozawa S.; Sawada J.
CS K. Sai, Division of Xenobiotic Metablism, Nat'l Inst. of Hlth. Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan. sai@nihs.go.jp
SO Drug Metabolism and Disposition, (2001) 29/11 (1505-1513).
Refs: 31
ISSN: 0090-9556 CODEN: DMDSAI
CY United States
DT Journal; Article
FS 022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Irinotecan (CPT-11) is an anticancer prodrug. It is converted by ***carboxylesterase*** to yield an active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which acts as a topoisomerase I inhibitor. Several oxidative metabolites of CPT-11 have been identified in humans, including 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin (APC) and 7-ethyl-10-(4-amino-1-piperidino)carbonyloxycamptothecin (NPC), generated by cytochrome P-450 3A4 (CYP3A4). Other minor metabolites in which metabolic pathways and biologic activities have not been identified also exist. To further investigate the metabolism of CPT-11 in human liver, we analyzed metabolites of CPT-11 in human hepatic microsomes using a high-performance liquid chromatography/mass spectrometry (HPLC/MS) system and detected a new metabolite that was the major one produced in the microsomal system. HPLC-tandem mass spectrometry (HPLC/MS/MS) analysis indicated that this compound was an oxidation product formed by the loss of two hydrogen atoms from the terminal piperidine ring. Kinetic analyses indicated that a single enzyme generated the metabolite, and we have identified this enzyme in two in vitro systems. The formation of the new metabolite was significantly inhibited by SKF525A, ketoconazole, and an anti-CYP3A4 antibody and catalyzed specifically by CYP3A4 expressed in insect microsomes. A significant correlation was observed between the generation of this metabolite and the CYP3A4 content in individual human hepatic microsomes. These findings indicate that this newly detected metabolite is a CYP3A4-generated product that may be produced in hepatic microsomes of patients treated with CPT-11.

L5 ANSWER 4 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS DUPLICATE 3
AN 2002:55266 BIOSIS
DN PREV200200055266
TI Identification and activities of human carboxylesterases for the activation of CPT-11, a clinically approved anticancer drug.
AU Senter, Peter D. (1); Beam, Kevin S.; Mixan, Bruce; Wahl, Alan F.
CS (1) Seattle Genetics, Inc., 21823 30th Drive SE, Bothell, WA, 98021: psenter@seagen.com USA
SO Bioconjugate Chemistry, (November December, 2001) Vol. 12, No. 6, pp. 1074-1080. http://pubs.acs.org/journals/bcches/. print.
ISSN: 1043-1802.
DT Article
LA English
AB CPT-11 is a clinically approved anticancer drug used for the treatment of advanced colorectal cancer. Upon administration, the carbamate side chain of the drug is hydrolyzed, resulting in the release of SN-38, an agent that has approximately 1000-fold increased cytotoxic activity. Since only a very small percentage of the injected dose of CPT-11 is converted to SN-38, there is a significant opportunity to improve its therapeutic efficacy and to diminish its systemic toxicity by selectively activating the drug within tumor sites. We envisioned that a mAb-human enzyme conjugate for CPT-11 activation would be of interest, particularly since the conjugate would likely be minimally immunogenic, and the prodrug is clinically approved. Toward this end, it was necessary to identify the most active human enzyme that could convert CPT-11 to SN-38. We isolated enzymes from human liver microsomes based on their abilities to effect the conversion and identified human ***carboxylesterase*** 2 (hCE-2) as having the greatest specific activity. hCE-2 was 26-fold more active than human ***carboxylesterase*** 1 and was 65% as active as rabbit liver ***carboxylesterase*** , the most active CPT-11 hydrolyzing enzyme known. The anti-p97 mAb 96.5 was linked to hCE-2, forming a conjugate that could bind to antigen-positive cancer cells and convert CPT-11 to SN-38. Cytotoxicity assays established that the conjugate led to the generation of active drug, but the kinetics of prodrug activation (48 pmol min-1 mg-1) was insufficient for immunologically specific prodrug activation. These results confirm the importance of hCE-2 for CPT-11 activation and underscore the importance of enzyme kinetics for selective prodrug activation.

L5 ANSWER 5 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001329715 EMBASE
TI Gilbert's syndrome - Clinical and pharmacological implications.
AU Radu P.; Atsmon J.
CS Dr. P. Radu, Clinical Research Center, Tel Aviv Sourasky, Medical Center, 6 Weizmann St., Tel Aviv 64239, Israel. qc@tasmc.health.gov.il
SO Israel Medical Association Journal, (2001) 3/8 (593-598).
Refs: 40
ISSN: 1565-1088 CODEN: IMAJCX
CY Israel
DT Journal; General Review
FS 048 Gastroenterology
022 Human Genetics
016 Cancer
037 Drug Literature Index
030 Pharmacology
038 Adverse Reactions Titles
005 General Pathology and Pathological Anatomy
017 Public Health, Social Medicine and Epidemiology
029 Clinical Biochemistry
LA English

L5 ANSWER 6 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 2001:460706 BIOSIS
DN PREV200100460706
TI Efficacy and toxicity of a CPT-11-based VDEPT method for purging: Preclinical studies focused on neuroblastoma.
AU Wagner, Lars M. (1); Wierdl, Monika (1); Harris, Linda C. (1); Potter, Philip M. (1); Danks, Mary K. (1)
CS (1) St. Jude Children's Research Hospital, Memphis, TN USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 453. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X.
DT Conference
LA English
SL English

L5 ANSWER 7 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 2001:440010 BIOSIS
DN PREV200100440010
TI Overexpression, purification and crystallization of a rabbit liver ***carboxylesterase*** that activates CPT-11.
AU Morton, Christopher L. (1); Bencharit, Sompop; Danks, Mary K.; Redinbo, Matthew R.; Potter, Philip M.
CS (1) St. Jude Children's Research Hospital, Memphis, TN USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 415. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X.
DT Conference
LA English
SL English

L5 ANSWER 8 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 2001:448790 BIOSIS
DN PREV200100448790
TI Steric constraints conferred by carboxylesterases determine the efficiency of CPT-11 conversion to SN-38.
AU Wadkins, Randy M. (1); Morton, Christopher L.; Weeks, James K.; Oliver, LaGora; Danks, Mary K.; Potter, Philip M.
CS (1) Johns Hopkins University School of Medicine, Baltimore, MD USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 415. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X.
DT Conference
LA English
SL English

L5 ANSWER 9 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 4
AN 2001260900 EMBASE
TI Structural constraints affect the metabolism of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) by carboxylesterases.
AU Wadkins R.M.; Morton C.L.; Weeks J.K.; Oliver L.; Wierdl M.; Danks M.K.; Potter P.M.
CS Dr. P.M. Potter, Department of Molecular Pharmacology, St. Jude Children's Res. Hospital, 332 N. Lauderdale, Memphis, TN 38105, United States. phil.potter@stjude.org
SO Molecular Pharmacology, (2001) 60/2 (355-362).
Refs: 37
ISSN: 0026-895X CODEN: MOPMA3
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin [CPT-11 (irinotecan)] is a water-soluble camptothecin-derived prodrug that is activated by esterases to yield the potent topoisomerase I poison SN-38. We identified a rabbit liver ***carboxylesterase*** (***CE***) that was very efficient at CPT-11 metabolism; however, a human homolog that was more than 81% identical to this protein activated the drug poorly. Recently, two other human CEs have been isolated that are efficient in the conversion of CPT-11 to SN-38, yet both demonstrate little homology to the rabbit protein. To understand this phenomenon, we have characterized a series of esterases from human and rabbit, including several chimeric proteins, for their ability to metabolize CPT-11. Computer predictive modeling indicated that the ability of each enzyme to activate CPT-11 was dependent on the size of the entrance to the active site. Kinetic studies with a series of nitrophenyl and naphthyl esters confirmed these predictions, indicating that activation of CPT-11 by a ***CE*** is constrained by size-limited access of the drug to the active site catalytic amino acid residues.

L5 ANSWER 10 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 5
AN 2001181508 EMBASE
TI Human plasma ***carboxylesterase*** and butyrylcholinesterase enzyme activity: Correlations with SN-38 pharmacokinetics during a prolonged infusion of irinotecan.
AU Guemei A.A.; Cottrell J.; Band R.; Hehman H.; Prudhomme M.; Pavlov M.V.; Grem J.L.; Ismail A.S.; Bowen D.; Taylor R.E.; Takimoto C.H.
CS C.H. Takimoto, Univ. of TX Hlth. Sci. Ctr. SA, Department of Medical Oncology, MSC 7884, 703 Floyd Curl Drive, San Antonio, TX 78229-3900, United States. takimotoc@oncology.uthscsa.edu
SO Cancer Chemotherapy and Pharmacology, Supplement, (2001) 47/4 (283-290).
Refs: 28
ISSN: 0943-9404 CODEN: CCHSET
CY Germany
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Purpose: To characterize the relationships between human plasma irinotecan ***carboxylesterase*** -converting enzyme activity, caboxylesterase-mediated hydrolysis of p-nitrophenyl acetate (pNPA), and the butyrylcholinesterase-mediated hydrolysis of butyrylthiocholine in human plasma and to test the ability of these in vitro tests to predict the variability in SN-38 pharmacokinetics in adult patients during a prolonged infusion of irinotecan. Methods: Individual plasma-converting enzyme activity was measured in 20 adult cancer patients participating in a pharmacokinetic and phase I clinical trial of a prolonged 96-h intravenous infusion of irinotecan. The pNPA and butyrylthiocholine hydrolysis in patient plasma was also assayed. Results: The irinotecan ***carboxylesterase*** -converting enzyme in human plasma had a V(max) of 89.9 .+-. 22.7 pmol/h per ml plasma and a Km of 207 .+-. 56 .mu.M (mean .+-. SD, n = 3). The mean value of the specific activity of this enzyme in 20 adult cancer patients was 10.08 .+-. 2.98 pmol/h per ml plasma ranging from 5.43 to 15.39 pmol/h per ml. The area-under-the-concentration-versus time curve (AUC) ratio of SN-38 to irinotecan (AUC(SN-38)/AUC(CPT-11)) was used to assess the relative SN-38 exposure to the active metabolite in individual patients. Pharmacokinetic variations in the relative exposure to SN-38 did not correlate with the measured ***carboxylesterase*** -converting enzyme activity nor with plasma butyrylcholinesterase activity in our patient population. However, it did correlate with the measured pNPA hydrolysis activity in patient plasma (r(2) = 0.350, P = 0.0124, n = 18). Conclusions: Determination of patient plasma pNPA hydrolysis activity may have utility in predicting SN-38 pharmacokinetics during prolonged infusions of irinotecan.

L5 ANSWER 11 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001033929 EMBASE
TI Prevention and management of chemotherapy-induced nausea and vomiting, part 1.
AU Beckwith M.C.; Mullin S.
CS Dr. M.C. Beckwith, Clinical Drug Information Specialist, University Hospitals and Clinics, Department of Pharmacy Services, 50 North Medical Drive A-050, Salt Lake City, UT 84132, United States
SO Hospital Pharmacy, (2001) 36/1 (67-80).
Refs: 66
ISSN: 0018-5787 CODEN: HOPHAZ
CY United States
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Credit - This lesson is good for 0.2 ***CE*** units, with a passing grade of 70%. Goal - The goal of this program is to inform the participant of cost-effective ways to prevent, identify, and manage nausea and vomiting induced by antineoplastic agents. Objectives - At the completion of this program the participant will be able to: 1. List antineoplastic agents associated with a high incidence of nausea and vomiting. 2. Identify patient-specific risk factors for developing chemotherapy-induced nausea and vomiting (CINV) and how these factors may influence treatment of this syndrome. 3. Compare the three major types of CINV, including the pathophysiologic mechanism, time of onset, and symptom duration of each type. 4. Explain the mechanism of action and appropriate place in therapy for each type of antiemetic agent. 5. Differentiate between pharmacologic regimens for the prevention and treatment of CINV in adults. 6. Identify drug-specific factors that must be considered in developing a formulary management strategy for the antiemetic agents. 7. Describe specific information that the pharmacist can share with patients to help them understand and manage CINV.

L5 ANSWER 12 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001283813 EMBASE
TI Practical implications of cytotoxic drug administration.
AU Van Den Brande J.; Vermorken J.B.
CS Dr. J. Van Den Brande, Department of Medical Oncology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium. Jan.Van.den.Brande@uza.uia.ac.be
SO CME Journal of Gynecologic Oncology, (2001) 6/1 (43-51).
Refs: 66
ISSN: 1219-9087 CODEN: CJGOFS
CY Hungary
DT Journal; General Review
FS 016 Cancer
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB There are different ways of delivering cytotoxic drugs to the tumor in cancer patients. An overview of intravenous, intra-arterial, subcutaneous/intramuscular, intraventricular/intrathecal, intraperitoneal, intrapleural/intrapericardial, intravesicular and intracerebral drug administration is provided. Possible complications, local and/or systemic, and their prevention and management are discussed. Attention is paid to ways of providing treatments on an ambulant basis.

L5 ANSWER 13 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001398875 EMBASE
TI Analytical approaches for traditional Chinese medicines exhibiting antineoplastic activity.
AU Tsai T.-H.
CS T.-H. Tsai, Nat'l Research Inst. of Chinese Med., Taipei 112, Taiwan,Province of China. thtsai@cma23.nricm.edu.tw
SO Journal of Chromatography B: Biomedical Sciences and Applications, (25 Nov 2001) 764/1-2 (27-48).
Refs: 190
ISSN: 0378-4347 CODEN: JCBBEP
PUI S 0378-4347(01)00277-8
CY Netherlands
DT Journal; General Review
FS 016 Cancer
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology

037 Drug Literature Index
039 Pharmacy
LA English
SL English
AB Traditional Chinese medicines have attracted great interest in recent researchers as alternative antineoplastic therapies. This review focuses on analytical approaches to various aspects of the antineoplastic ingredients of traditional Chinese medicines. Emphasis will be put on the processes of biological sample extraction, separation, clean-up steps and the detection. The problems of the extraction solvent selection and different types of column chromatography are also discussed. The instruments considered are gas chromatography, capillary electrophoresis (***CE***) and high-performance liquid chromatography (HPLC) connected with various detectors (ultraviolet, fluorescence, electrochemistry, mass, etc.). In addition, determinations of antineoplastic herbal ingredients, including camptothecin, taxol (paclitaxel), vinblastine, vincristine, podophyllotoxin, colchicine, and their related compounds, such as irinotecan, SN-38, topotecan, 9-aminocamptothecin, docetaxel (taxotere) and etoposide, are briefly summarized. These drugs are structurally based on the herbal ingredients, and some of them are in trials for clinical use. Evaluation of potential antineoplastic herbal ingredients, such as harringtonine, berberine, emodin, genistein, berbamine, daphnoretin, and irisquinone, are currently investigated in laboratories. Other folk medicines are excluded from this paper because their antineoplastic ingredients are unknown. .COPYRGT. 2001 Elsevier Science B.V. All rights reserved.

L5 ANSWER 14 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 6
AN 2000329273 EMBASE
TI Proficient metabolism of irinotecan by a human intestinal ***carboxylesterase*** .
AU Khanna R.; Morton C.L.; Danks M.K.; Potter P.M.
CS P.M. Potter, Department of Molecular Pharmacology, St. Jude Children's Res. Hospital, 332 North Lauderdale Street, Memphis, TN 38105, United States. phil.potter@stjude.org
SO Cancer Research, (1 Sep 2000) 60/17 (4725-4728).
Refs: 26
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Irinotecan [7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin (CPT-11)] is metabolized by esterases to yield the potent topoisomerase I poison 7-ethyl-10-hydroxycamptothecin. One of the major side effects observed with CPT-11 is gastrointestinal toxicity, and we supposed that this might be due to local activation of CPT-11 within the gut. ***Carboxylesterase*** (***CE***) activity was detected in human gut biopsies, and extracts of these tissues converted CPT-11 to 7-ethyl-10-hydroxycamptothecin in vitro. Expression of a human intestinal ***CE*** cDNA in COS-7 cells produced extracts that demonstrated proficient CPT-11 activation and conferred sensitivity of cells to CPT-11. These results suggest that gut toxicity from CPT-11 may be due in part to direct drug conversion by CEs present within the small intestine.

L5 ANSWER 15 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000326368 EMBASE
TI Factors involved in prolongation of the terminal disposition phase of SN-38: Clinical and experimental studies.
AU Kehrer D.F.S.; Yamamoto W.; Verweij J.; De Jonge M.J.A.; De Bruijn P.; Sparreboom A.
CS A. Sparreboom, Department of Medical Oncology, Rotterdam Cancer Institute, University Hospital Rotterdam, P. O. Box 5201, 3008 AE Rotterdam, Netherlands. sparreboom@onch.azr.nl
SO Clinical Cancer Research, (2000) 6/9 (3451-3458).
Refs: 48
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The active metabolite of irinotecan (CPT-11), 7-ethyl-10-hydroxycamptothecin (SN-38), is either formed through enzymatic cleavage of CPT-11 by carboxyl esterases (CEs) or through cytochrome P-450 3A-mediated oxidation to 7-ethyl-10-[4-(1-piperidino)-1-amino] carbonyloxycamptothecin (NPC) and a subsequent conversion by ***CE*** . In the liver, SN-38 is glucuronidated (SN-38G) by UGT1A1, which also conjugates bilirubin. Fourteen patients were treated with 350 mg/m2 CPT-11, and we performed pharmacokinetic analysis during a 500-h collection period. The half-life and area under the plasma concentration-time curve of SN-38 were 47 .+-. 7.9 h and 2.0 .+-. 0.79 .mu.M.cntdot.h, respectively, both representing a 2-fold increase as compared with earlier reported estimates (A. Sparreboom et al., Clin. Cancer Res., 4: 2747-2754, 1998). As an explanation for this phenomenon, we noted substantial formation of SN-38 from CPT-11 and NPC by plasma ***CE*** , consistent with the low circulating levels of NPC observed. In addition, transport studies in Caco-2 monolayers indicated that nonglucuronidated SN-38 could cross the membrane from apical to basolateral, indicating the potential for recirculation processes that can prolong circulation times. Interestingly, individual levels of fecal .beta.-glucuronidase, which is known to mediate SN-38G hydrolysis, were not related to any of the SN-38 kinetic parameters (r = 0.09; P = 0.26), suggesting flint interindividual variation in this enzyme is unimportant in explaining SN-38 pharmacokinetic variability. We have also found, in contrast to earlier data, that SN-38G/SN-38 plasma concentration ratios decrease over time from .apprx.7 (up to 50 h) to .apprx. 1 (at 500 h). This decrease could be explained by the fact that glucuronidation of SN-38 and bilirubin is increasingly competitive at lower drug levels. In addition, no evidence was found for SN-38G transport through the Caco-2 cells. Our findings indicate that until now the circulation time of SN-38 has been underestimated. This is of crucial importance to our understanding of the clinical action of CPT-11 and for future pharmacokinetic/pharmacodynamic relationships.

L5 ANSWER 16 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 7
AN 2000101515 EMBASE
TI Characterization of CPT-11 hydrolysis by human liver ***carboxylesterase*** isoforms hCE-1 and hCE-2.
AU Humerickhouse R.; Lohrbach K.; Li L.; Bosron W.F.; Dolan M.E.
CS M.E. Dolan, University of Chicago Medical Center, Section of Hematology/Oncology, Box MC2115, 5841 South Maryland Avenue, Chicago, IL 60637-1470, United States. edolan@medicine.bsd.uchicago.edu
SO Cancer Research, (1 Mar 2000) 60/5 (1189-1192).
Refs: 20
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB 7-Ethyl.10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecin (irinotecan; CPT-11) is a prodrug activated by ***carboxylesterase*** enzymes. We characterized the hydrolysis of CPT-11 by two recently identified human ***carboxylesterase*** (hCE) enzymes, hCE-1 and hCE-2. K(m) and V(max) for hCE-1 and hCE-2 are 43 .mu.M and 0.53 nmol/min/mg protein and 3.4 .mu.M and 2.5 nmol/min/mg protein, respectively. hCE-2 has a 12.5-fold higher affinity for CPT-11 and a 5-fold higher maximal rate of CPT-11 hydrolysis when compared with hCE-1. In cytotoxicity assays, incubation of 1 .mu.M CPT-11 with hCE-2 (3.6 .mu.g/ml) resulted in a 60% reduction in survival of SQ20b cells. No significant reduction in cell survival was observed after incubation of CPT- 11 with hCE-1. These data indicate that hCE-2 is a high-affinity, high- velocity enzyme with respect to CPT-11. hCE-2 likely plays a substantial role in CPT-11 activation in human liver at relevant pharmacological concentrations.

L5 ANSWER 17 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 2000:264561 BIOSIS
DN PREV200000264561
TI Characterization of CPT-11 hydrolysis by human liver ***carboxylesterase*** isoforms hCE-1 and hCE-2.
AU Humerickhouse, Rod A. (1); Lohrbach, Karen; Li, Lin; Bosron, William F.; Dolan, M. Eileen
CS (1) Indiana Univ Sch of Medicine, Indianapolis, IN USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 701. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DT Conference
LA English
SL English

L5 ANSWER 18 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 2000:264514 BIOSIS
DN PREV200000264514
TI Development of adenovirus expressing a secreted rabbit liver ***carboxylesterase*** for vdept with CPT-11.
AU Wierdl, Monika (1); Morton, C. L. (1); Potter, P. M. (1)
CS (1) St. Jude Children's Res Hosp, Memphis, TN USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 671. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DT Conference
LA English
SL English

L5 ANSWER 19 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000315021 EMBASE
TI Characterization of CPT-11 converting ***carboxylesterase*** activity in colon tumor and normal tissues: Comparison with p-nitro-phenylacetate converting ***carboxylesterase*** activity.
AU Hennebelle I.; Terret C.; Chatelut E.; Bugat R.; Canal P.; Guichard S.
CS S. Guichard, Laboratoire de Pharmacologie, Institut Claudius Regaud, 20

rue du Pont Saint-Pierre, 31052 Toulouse Cedex, France.
guichard@icr.fnclcc.fr
SO Anti-Cancer Drugs, (2000) 11/6 (465-470).
Refs: 26
ISSN: 0959-4973 CODEN: ANTDEV
CY United Kingdom
DT Journal; Article
FS 016 Cancer
029 Clinical Biochemistry
LA English
SL English
AB Irinotecan (CPT-11) is a topoisomerase I inhibitor commonly used in the treatment of colorectal tumors. It is a prodrug, converted to an active metabolite, SN-38, by carboxylesterases (CEs). CEs are ubiquitary enzymes that react with numerous substrates. A specific CPT-11 converting enzyme was isolated from rat serum, with different kinetic properties than other CEs. We determined kinetic properties of specific CPT-11 ***CE*** activity (CPT- ***CE***) in human normal liver and colon tumors. K(m) were very similar (3.4 .mu.M in liver and 3.8 .mu.M in colon tumors), but V(max) was higher in liver (2.7 pmol/min/mg protein) than in colon tumor (1.7 pmol/min/mg protein). CPT- ***CE*** and total ***CE*** (using p-nitro-phenylacetate as substrate) were weakly correlated in colon tumors. The large interpatient variability observed in liver CPT- ***CE*** activity could play a potential role in the pharmacokinetic variability observed with irinotecan: (C) 2000 Lippincott Williams and Wilkins.

L5 ANSWER 20 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 2000:224981 BIOSIS
DN PREV200000224981
TI Purging of neuroblastoma cells from hematopoietic cells with adenovirus, rabbit ***carboxylesterase*** and CPT-11 prior to autologous stem cell rescue.
AU Meck, M. M. (1); Harris, L. C. (1); Houghton, P. J. (1); Potter, P. M. (1); Danks, Mary K. (1)
CS (1) St Jude Children's Res Hosp, Memphis, TN USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 465.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DT Conference
LA English
SL English

L5 ANSWER 21 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001022279 EMBASE
TI Pharmacokinetics of orally administered camptothecins.
AU Gupta E.; Vyas V.; Ahmed F.; Sinko P.; Cook T.; Rubin E.
CS E. Gupta, Bristol-Myers Squibb, Mail Stop D13-04, PO Box 4000, Princeton, NJ 08543, United States
SO Annals of the New York Academy of Sciences, (2000) 922/- (195-204).
Refs: 13
ISSN: 0077-8923 CODEN: ANYAA
CY United States
DT Journal; Conference Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Phase I trials of oral camptothecins, including camptothecin (CPT) and irinotecan (CPT-11), have reported substantial interpatient variability in systemic exposure, which could result in suboptimal antitumor activity in some patients or enhanced risk for toxicity in others. This investigation evaluates the contribution of intestinal absorption and first-pass metabolism in the disposition of oral CPT and CPT-11, respectively. The transport of CPT in Caco-2 cell lines (validated model of intestinal drug transport) was concentration dependent and saturable (V(max): 34x10(-5) cm/sec and K(m): 20 .mu.M), and was temperature dependent with an activation energy (E(a)) of 11.7 kcal/mole. Cumulatively, this data was indicative of carrier-mediated intestinal transport. In addition, a reduction of transport in the presence of sodium azide plus deoxyglucose suggested ATP dependence. Thus, variable expression and availability of intestinal transporters could contribute to the observed wide variability in the exposure to oral CPT. CPT-11 is hydrolyzed by the ubiquitous enzyme carboxyl esterase to active SN-38, and first-pass metabolism of oral CPT-11 would include both intestinal and hepatic hydrolysis. Incubation of CPT-11 with S9 fractions of human liver and intestinal tissues resulted in variable rates of formation of SN-38. The mean (.+-.SD) specific activities (pmoles/min/mg) were: liver (8.57 .+-. 10.4, n = 8), duodenum (5.08 .+-. 3.7, n = 4), jejunum (6.44 .+-. 2.8, n = 5), ileum (4.81 .+-. 2.4, n = 5), colon (1.93 .+-. 1.5, n = 6), and rectum (0.82, n = 1). Interestingly, there was a decrease in SN-38 formation by tumor tissue compared to matched normal liver and colon tissues. Therefore variable first-pass metabolism could contribute to the substantial differences in the systemic exposures to CPT-11 and SN-38 in patients receiving oral CPT-11.

L5 ANSWER 22 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000266453 EMBASE
TI New therapeutic agents in the treatment of recurrent high-grade gliomas.
AU Brandes A.A.; Pasetto L.M.
CS A.A. Brandes, Divisione di Oncologia Medica, Azienda Ospedale, Universita di Padova, Via Giustiniani 2, 35100 Padova, Italy
SO FORUM - Trends in Experimental and Clinical Medicine, (2000) 10/2 (121-131).
Refs: 51
ISSN: 1121-8142 CODEN: FTCME2
CY Italy
DT Journal; General Review
FS 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The incidence of central nervous system neoplasias ranges from 3.8 to 5.1 cases per 100,000 inhabitants. In the presence of recurrence, the treatment is problematic; chemotherapy is experimental, primarily because the response is palliative and of limited duration. This article analyses the new drugs that have been introduced in the treatment of these patients in the latest years, the objective response, the time to progression and the mean survival time. The most encouraging results to date come from studies of temozolomide, which is one of the most active and best tolerated drugs in recent years. New approaches to the chemotherapy treatment are necessary. Enrolment of patients into rigorous, well-conducted, clinical trials, both at tumour diagnosis and after tumour recurrence, will generate new information regarding investigational therapies and may offer improved therapies for patients with malignant gliomas.

L5 ANSWER 23 OF 83 CAPLUS COPYRIGHT 2002 ACS
AN 2000:521283 CAPLUS
DN 133:227657
TI Effective prodrug liposome and conversion to active metabolite
AU Sadzuka, Y.
CS University of Shizuoka, Shizuoka, 422-8526, Japan
SO Curr. Drug Metab. (2000), 1(1), 31-48
CODEN: CDMUBU
PB Bentham Science Publishers Ltd.
DT Journal
LA English
AB Some antitumor agents encapsulated in liposomes have been used clin. However, the usefulness of liposomes is limited to the liposomalization of active compds. Irinotecan hydrochloride (CPT-11) is a prodrug of closed lactone ring form of SN-38, which is an active metabolite with antitumor activity and side toxicity. The plasma concns. of closed CPT-11 and SN-38 increased with the liposomalization, and their blood circulation was prolonged by the polyethylene glycol (PEG) modification. The antitumor activity of CPT-11 increased due to the elevated tumor distribution of closed CPT-11 and SN-38 levels by the PEG-modified liposomes. In the tumor, CPT-11 was converted to SN-38. Thus, it is considered that passive targeting to the tumor by liposomalization elevated the SN-38 level in the tumor esp. and increased the antitumor activity of CPT-11. The closed/total ratio of SN-38 in the tumors of the liposomes group was greater than that of the CPT-11 soln. group. Namely, SN-38 was thought to be generated in intact liposomes contg. CPT-11. The generation of SN-38 in the liposomal membrane was shown after the incubation of liposome contg. CPT-11 with ***carboxylesterase*** . It is therefore considered that part of CPT-11 is converted to SN-38 in intact liposomes. Furthermore, intestinal disorder, a side toxicity of CPT-11, decreased to depend on the closed SN-38 concns. in the bile by liposomalization. Although the liposomes induce the improved tissue distribution of the prodrug, the tissue distribution of active metabolites do not always improve. However, CPT-11 entrapped liposome was useful.
RE.CNT 57
RE
(1) Allen, T; Biochem Biophys Acta 1989, V981, P27 CAPLUS
(2) Allen, T; Biochem Biophys Acta 1991, V1066, P29 CAPLUS
(3) Allen, T; FEBS Lett 1987, V223, P42 CAPLUS
(4) Araki, E; Jpn J Cancer Res 1993, V84, P697 CAPLUS
(5) Bangham, A; J Mol Biol 1965, V13, P238 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 24 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 2001:172674 BIOSIS
DN PREV200100172674
TI Sensitization of human tumor cells to CPT-11 by adenoviral-mediated delivery of a rabbit liver ***carboxylesterase*** .
AU Wierdl, Monika (1); Morton, Christopher L. (1); Weeks, James K. (1); Danks, Mary K. (1); Harris, Linda C. (1); Potter, Philip M. (1)
CS (1) Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, 38105 USA
SO Cancer Gene Therapy, (December, 2000) Vol. 7, No. 12, pp. S22. print.
Meeting Info.: Ninth International Conference on Gene Therapy of Cancer San Diego, California, USA December 07-09, 2000
ISSN: 0929-1903.
DT Conference
LA English
SL English

L5 ANSWER 25 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000206357 EMBASE
TI Preclinical evaluation of irinotecan.
CS U. Vanhoefer, Department of Internal Medicine, West German Cancer Center,

University of Essen Medical School, D-45122 Essen. ud.vanhoefer@uni-essen.de
SO Onkologie, (2000) 23/SUPPL. 4 (2-7).
Refs: 100
ISSN: 0378-584X CODEN: ONKOD2
CY Germany
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English; German
AB DNA topoisomerase I (TOP-I) is a ubiquitous nuclear enzyme, which plays a key role in cellular processes like DNA replication and transcription. With the realization that TOP-I is an important target in cancer therapy, TOP-I interactive agents entered intensive preclinical and clinical evaluation programs. Irinotecan is enzymatically converted by ***carboxylesterase*** to its most active cytotoxic metabolite 7-ethyl-10-hydroxy-camptothecin (SN-38), which is inactivated by hepatic biotransformation in a sequential metabolism. SN-38 establishes an equilibrium between the pharmacologically active closed lactone ring and the inactive hydroxy acid-form by reversible pH-dependent hydrolysis. SN-38 exerts its cytotoxic mechanism by generating intermediate forms of drug-stabilized covalent DNA/TOP-I complexes, which may lead by collision with the moving replication complexes to arrest and disassembly of the replication machinery. In preclinical models, acquired resistance to camptothecin derivatives has been mainly related to down-regulation of TOP-I expression as well as to alterations in structure and function of the TOP-I gene. Based on promising preclinical data on synergistic cytotoxic drug interactions, a variety of irinotecan-based combinations are currently under clinical evaluation (e.g., cisplatin, oxaliplatin, raltitrexed, taxanes). The task of future investigations will be to identify molecular markers, which are predictive for tumor response to irinotecan-based chemotherapy.

L5 ANSWER 26 OF 83 CAPLUS COPYRIGHT 2002 ACS
AN 1999:549389 CAPLUS
DN 131:165300
TI Rabbit liver ***carboxylesterase*** capable of activating chemotherapeutic prodrug and thereby sensitizing and inhibiting growth of human tumor cells
IN Danks, Mary K.; Potter, Philip M.; Houghton, Peter J.
PA St. Jude Children's Research Hospital, USA
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9942593	A1	19990826	WO 1999-US3171	19990212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9928679	A1	19990906	AU 1999-28679	19990212
EP 1054979	A1	20001129	EP 1999-909488	19990212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1998-75258 A2 19980219
WO 1999-US3171 W 19990212
AB Polynucleotides encoding a ***carboxylesterase*** enzyme and polypeptides encoded by the polynucleotides which are capable of metabolizing the chemotherapeutic prodrug CPT-11 (Irinotecan) and its inactive metabolite APC to active SN-38 drug (7-ethyl-10-hydroxycamptothecin) are provided. Complementary DNA encoding a ***carboxylesterase*** was cloned from rabbit liver and shown to differ from the published sequence (G. Kurza and J. Ozois, 1988) of rabbit liver ***carboxylesterase*** . This enzyme was 60-fold more active with CPT-11 than the endogenous human enzyme, and use of this enzyme in combination with APC renders the inactive metabolite a useful chemotherapeutic prodrug. Compns. comprising a polynucleotide of the present invention and a disease-specific responsive promoter (e.g., the ornithine decarboxylase promoter responsive to c-myc) can be delivered to selected tumor cells to sensitize the tumor cells to the chemotherapeutic prodrug CPT-11, thereby inhibiting tumor cell growth. Another method for delivering the ***carboxylesterase*** to selected tumor cells involves antibody direct enzyme prodrug therapy (ADEPT). Rabbit ***carboxylesterase*** /prodrug compns. can also be used to purge bone marrow of tumor cells, thereby preventing minimal residual disease. In addn., screening assays for identification of drugs activated by this enzyme are described.
RE.CNT 9
RE
(1) Alexson, S; J Biol Chem 1994, V269(25), P17118 CAPLUS
(2) Danks, M; Cancer Research 1998, V58, P20 CAPLUS
(3) Miller, S; J Biol Chem 1980, V255(15), P7161 CAPLUS
(4) Mullen; WO 93/01281 A1 1993 CAPLUS
(5) Potter, P; Cancer Research 1998, V58, P2646 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 27 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999251314 EMBASE
TI Water soluble 20(S)-glycinate esters of 10,11- methylenedioxycamptothecins are highly active against human breast cancer xenografts.
AU Wadkins R.M.; Potter P.M.; Vladu B.; Marty J.; Mangold G.; Weitman S.; Manikumar G.; Wani M.C.; Wall M.E.; Von Hoff D.D.
CS R.M. Wadkins, Cancer Therapy and Research Center, Institute for Drug Development, 14960 Omicron Drive, San Antonio, TX 78245, United States. rwadkins@saci.org
SO Cancer Research, (15 Jul 1999) 59/14 (3424-3428).
Refs: 33
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Water-soluble 20(S)-glycinate esters of two highly potent 10,11-methylenedioxy analogues of camptothecin (CPT) have been synthesized and evaluated for their ability to eradicate human breast cancer tumor xenografts. The glycinate ester moiety increases the water solubility of the 10,11-methylenedioxy analogues 4-16-fold. However, in contrast to CPT11, a water-soluble CPT analogue that was recently approved for second line treatment of colorectal cancer, the 20(S)-glycinate esters do not require ***carboxylesterase*** for conversion to their active forms. The glycinate esters are hydrolyzed to their parent, free 20(S)-hydroxyl active analogues in phosphate buffer (pH 7.5) and in mouse and human plasma. The glycinate esters are also 20-40-fold less potent than CPT-11 in inhibiting human acetylcholinesterase. In vivo, we examined 20(S)-glycinate-10,11- methylenedioxycamptothecin, 20(S)-glycinate-7-chloromethyl-10,11- methylenedioxycamptothecin, and CPT-11. We found that the two 10,11- methylenedioxy analogues had antitumor activity against breast cancer xenografts that was comparable to that of CPT-11. Our results indicate that water-soluble 20(S)-glycinate esters of highly potent CPT analogues provide compounds that maintain biological activity, do not require interactions with carboxylesterases, and do not inhibit human acetylcholinesterase.

L5 ANSWER 28 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999291797 EMBASE
TI In vitro activation of Irinotecan to SN-38 by human liver and intestine.
AU Ahmed F.; Vyas V.; Cornfield A.; Goodin S.; Ravikumar T.S.; Rubin E.H.; Gupta E.
CS E. Gupta, B.MyersSquibb Pharmaceut. Res. Inst., PO Box 4000, Mail Stop D13-04, Princeton, NJ 08540, United States. guptae@bms.com
SO Anticancer Research, (1999) 19/3 A (2067-2071).
Refs: 24
ISSN: 0250-7005 CODEN: ANTRD4
CY Greece
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB Background: Irinotecan (CPT-11) is hydrolyzed by carboxyl esterase to the active metabolite SN-38 and oral irinotecan could undergo intestinal and hepatic activation. Materials and Methods: Irinotecan was incubated with S9 fractions of human liver and intestinal tissues and the specific activity was determined based on the formation rate of SN-38. Results: Irinotecan was hydrolyzed to SN-38 by hepatic and intestinal S9 fractions with mean (+-. SD) specific activities (pmoles/min/mg) of: liver (8.57 .+-. 10.4, n = 8), duodenum (5.06 .+-. 3.7, n = 4), jejunum (6.44 .+-. 2.8, n = 5), ileum (4.81 .+-. 2.4, n = 5), colon (1.93 .+-. 1.5, n = 6) and rectum (0.82, n = 1). When incubated with S9 fractions obtained from tumor tissues, there appeared to be a decrease in SN-38 formation compared to matched normal liver and colon tissues. Conclusion: Irinotecan undergoes conversion to its active metabolite in human intestinal S9 fractions and there is variability in the extent of SN-38 formation. The localized intestinal activation of irinotecan to SN-38 may provide a rationale for the development of oral irinotecan for gastrointestinal malignancies but could also cause mucosal damage leading to toxicity.

L5 ANSWER 29 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999380287 EMBASE
TI Sequence-dependent growth inhibition and DNA damage formation by the irinotecan-5-fluorouracil combination in human colon carcinoma cell lines.
AU Mans D.R.A.; Grivicich I.; Peters G.J.; Schwartsmann G.
CS D.R.A. Mans, SOAD, Hospital de Clinicas de Porto Alegre, Rua Ramiro Barcelos, Porto Alegre 2350, Brazil. fsoad@hcpa.ufrgs.br
SO European Journal of Cancer, (1999) 35/13 (1851-1861).
Refs: 51
ISSN: 0959-8049 CODEN: EJCAEL
PUI S 0959-8049(99)00222-1
CY United Kingdom
DT Journal; Article
FS 016 Cancer
029 Clinical Biochemistry

030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB We evaluated irinotecan (CPT-11) together with 5-fluorouracil (5-FU) for improved cell growth inhibition with respect to that by either agent alone in the human colon carcinoma cell lines SW620, HT-29 and SNU-C4. Cells were exposed for 24 h to each drug, as well as to various combinations and sequences of low, fixed doses of one drug with higher varying doses of the other, cultured for two more days in drug-free medium and then assessed for growth response with the sulphorhodamine B assay. Multiple drug effect analysis was used to evaluate the data, which were then related to the amount of DNA damage occurring in the cells which was determined by a fluorescence- enhancement assay for DNA unwinding. Cellular responses were also related to thymidylate synthase topoisomerase I and carboxyl esterase activities, which were assessed by a ligand-binding and a 3H-release assay; a DNA decatenation assay; and a spectrophotometric method, respectively. IC50 values for 5-FU alone in the SW620, HT29 and SNU-C4 cells were 15.3 .+-. 0.8, 8.2 .+-. 1.3 and 2.2 .+-. 0.7 .mu.M, respectively, and for CPT-11 2.0 .+-. 0.9, 2.5 .+-. 0.5 and 3.8 .+-. 0.3 .mu.M, respectively. The differential responses to 5-FU alone were possibly determined by differences in substrate affinity and conversion rate of thymidylate synthase (K(m) of approximately 7.5, 5.0 and 2.5 .mu.M and V0 of approximately 800, 200 and 2400 .mu.M/h, respectively). The comparable cellular responses to CPT-11 alone might be accounted for by the counterbalancing effects of differences in topoisomerase I (1, 1, and 1.5 arbitrary units, respectively) and carboxyl esterase activities (5055 .+-. 1789, 4080 .+-. 752, 1713 .+-. 522 mU/mg, respectively). IC20 CPT-11 prior to 5-FU was additive to synergistic in SW620, HT-29 and SNU-C4 cells (CIs of 0.7 .+-. 0.1). By contrast, pretreatment with IC20 5-FU antagonised the CPT-11- mediated growth inhibition (CIs of 1.9 .+-. 0.4, 1.7 .+-. 1.1, 2.5 .+-. 0.9, respectively). Simultaneous drug treatment did not produce more cell growth inhibition than either drug alone in the SW620 and the HT-29 cells, but was additive or antagonistic in the SNU-C4 cells (CIs of 1.1 .+-. 0.3 and 2.2 .+-. 1.4), depending on the ratio of the drugs. Increased DNA damage in the SW620 and HT-29 cells was only seen when IC20 CPT-11 preceded IC50 5-FU, resulting in approximately 40 and 25%, respectively, more lesions than for IC50 5-FU alone. In the SNU-C4 cells, not only such a treatment, but also simultaneous drug treatment produced (30 to 60%) more DNA damage than either drug alone. Our results show clear sequence-dependent antiproliferative effects and DNA damage formation by CPT-11 and 5-FU at combinations of low, fixed doses with higher, varying doses in cultured human colon carcinoma cells, and may be of relevance to the design of improved chemotherapeutic regimens in this disease.

L5 ANSWER 30 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 8
AN 1999137356 EMBASE
TI Comparison of activation of CPT-11 by rabbit and human carboxylesterases for use in enzyme/prodrug therapy.
AU Danks M.K.; Morton C.L.; Krull E.J.; Cheshire P.J.; Richmond L.B.; Naeve C.W.; Pawlik C.A.; Houghton P.J.; Potter P.M.
CS P.M. Potter, Department of Molecular Pharmacology, St. Jude Children's Res. Hospital, 332 North Lauderdale, Memphis, TN 38105, United States. phil.potter@stjude.org
SO Clinical Cancer Research, (1999) 5/4 (917-924).
Refs: 31
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Article
FS 016 Cancer
022 Human Genetics
037 Drug Literature Index
LA English
SL English
AB Several recent studies have examined the possibility of producing tumor-specific cytotoxicity with various enzyme/ prodrug combinations. The enzymes are targeted to tumor cells either with antibodies (ADEPT, antibody directed enzyme prodrug therapy) or with viruses (VDEPT). The goal of the present study was to identify an appropriate enzyme for use in activating the prodrug 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11). In this study, we compared the efficiency of CPT-11 metabolism by rabbit and human carboxylesterases in in vitro and in situ assays. Although the rabbit and human enzymes are very similar (81% identical; 86% homologous) and the active site amino acids are 100% identical, the rabbit enzyme was 100-1000- fold more efficient at converting CPT-11 to SN-38 in vitro and was 12-55- fold more efficient in sensitizing transfected cells to CPT-11. In vivo, Rh30 rhabdomyosarcoma cells expressing the rabbit ***carboxylesterase*** and grown as xenografts in immune-deprived mice were also more sensitive to CPT-11 than were control xenografts or xenografts expressing the human enzyme. Each of the three types of xenografts regressed when the mice were treated with CPT- 11 given i.v. at 2.5 mg of CPT-11/kg/daily for 5 days/week for 2 weeks [(dx5)2] (one cycle of therapy), repeated every 21 days for a total of three cycles. However, following cessation of treatment, recurrent tumors were detected in seven of seven mice bearing control Rh30 xenografts and in two of seven mice bearing Rh30 xenografts that expressed the human enzyme. No tumors recurred in mice bearing xenografts that expressed the rabbit ***carboxylesterase*** . We conclude that rabbit ***carboxylesterase*** /CPT-11 may be a useful enzyme/prodrug combination.

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=> d his

(FILE 'HOME' ENTERED AT 13:18:00 ON 17 JAN 2002)

FILE 'REGISTRY' ENTERED AT 13:18:08 ON 17 JAN 2002
L1 4 S IRINOTECAN
L2 1 S CPT-11

FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 13:24:14 ON 17 JAN 2002
L3 3200 S L2
L4 133 S L3 AND (CARBOXYLESTERASE OR CE)
L5 83 DUP REM L4 (50 DUPLICATES REMOVED)

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FILE 'STNGUIDE' ENTERED AT 13:31:36 ON 17 JAN 2002

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L5 ANSWER 31 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999312780 EMBASE
TI Recent developments in gene-directed enzyme prodrug therapy (GDEPT) for cancer.
AU Niculescu-Duvaz I.; Cooper R.G.; Stribbling S.M.; Heyes J.A.; Metcalfe J.A.; Springer C.J.
CS I. Niculescu-Duvaz, CRC Centre for Cancer Therapeutics, Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom.
cspringer@icr.ac.uk
SO Current Opinion in Molecular Therapeutics, (1999) 1/4 (480-486).
Refs: 61
ISSN: 1464-8431 CODEN: CUOTFO
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
022 Human Genetics
037 Drug Literature Index
LA English
SL English
AB Gene-directed enzyme prodrug therapy (GDEPT) is a promising two-step treatment for solid malignant tumors. In the first step, the gene for a foreign enzyme is administered and directed to the tumor, where it may be expressed using specific transcriptional elements. In the second step, prodrugs are administered and activated by the foreign enzyme expressed at the tumor. This review focuses on the progress from the end of 1997 to date. Important issues, such as viral and non-viral vectors, new enzyme/prodrug systems, new strategies, advances in the understanding of the bystander effects, the comparison of different systems used in GDEPT and clinical trials are outlined.

L5 ANSWER 32 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 9
AN 1999160921 EMBASE
TI CPT-11 converting ***carboxylesterase*** and topoisomerase I activities in tumour and normal colon and liver tissues.
AU Guichard S.; Terret C.; Hennebelle I.; Lochon I.; Chevreau P.; Fretigny E.; Selves J.; Chatelut E.; Bugat R.; Canal P.
CS P. Canal, Groupe Pharmacol. Clin. Experimental, Institut Claudius Regaud, 20-24 rue de Pont Saint Pierre 31052, Toulouse Cedex, France
SO British Journal of Cancer, (1999) 80/3-4 (364-370).
Refs: 43
ISSN: 0007-0920 CODEN: BJCAAI
CY United Kingdom
DT Journal; Article
FS 016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB CPT-11 is a prodrug activated by carboxylesterases to the active metabolite SN-38 which is a potent inhibitor of topoisomerase I. CPT-11 is of clinical interest in the treatment of colorectal cancer. We evaluated the activities of CPT-11 converting ***carboxylesterase*** (CPT- ***CE***) and topoisomerase I (topo I) in 53 colorectal tumours, in eight liver metastases and in normal tissue adjacent to the tumours. Both CPT- ***CE*** and topo I activities were widely variable in the malignant and the normal tissue of patients with colorectal carcinomas. CPT- ***CE*** was only two to threefold lower in primary tumours compared to normal liver, suggesting that a local conversion to SN-38 might occur in tumour cells. CPT- ***CE*** was similar in liver and in normal colon tissues. Levels of topo I in tumour ranged from 580 to 84900 U mg protein-1 and was above 40000 U mg protein-1 in 11 of 53 patients. Similarly, a very high ratio (> 5) between tumour and normal tissues were observed in 12 of 53 patients. An inverse correlation was observed between the topo I activity and the clinical stage of disease. Clinical studies are in progress in our institution to explore a possible relationship between CPT- ***CE*** and topo I activities in tumour cells and the response to CPT-11-based chemotherapy in patients with colorectal cancer.

L5 ANSWER 33 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1999:179140 BIOSIS
DN PREV199900179140
TI CPT-11 converting ***carboxylesterase*** in tumor and normal colon and liver tissues.
AU Guichard, S.; Hennebelle, I.; Chevreau, P.; Fretigny, E.; Selves, J.; Bugat, R.; Canal, P.
CS Inst. Claudius Regaud, Clin. Parc Sarrus, CHU Purpan, Toulouse France
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 340.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research
. ISSN: 0197-016X.
DT Conference
LA English

L5 ANSWER 34 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 10
AN 1999113767 EMBASE
TI High-performance liquid chromatographic method for the simultaneous determination of the camptothecin derivative irinotecan hydrochloride, CPT-11, and its metabolites SN-38 and SN-38 glucuronide in rat plasma with a fully automated on-line solid-phase extraction system, PROSPEKT.
AU Kurita A.; Kaneda N.
CS A. Kurita, Yakult Central Institute, Microbiological Research, 1796 Yaho, Kunitachi, Tokyo 186-8650, Japan
SO Journal of Chromatography B: Biomedical Sciences and Applications, (1999) 724/2 (335-344).
Refs: 22
ISSN: 0378-4347 CODEN: JCBBEP
PUI S 0378-4347(98)00554-4
CY Netherlands
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB We established a high-performance liquid chromatography (HPLC) method for the simultaneous determination of the camptothecin (CPT) derivative, irinotecan hydrochloride (CPT-11) and its metabolites, 7-ethyl-10-hydroxycamptothecin (SN-38) and SN-38 glucuronide (SN-38G) in rat plasma with a fully automated on-line solid-phase extraction system, PROSPEKT. Plasma samples were pretreated with 0.146 M H3PO4 to inactivate
carboxylesterase and .beta.-glucuronidase in rat plasma, and added with the internal standard solution (0.146 M H3PO4 containing 1 .mu.g/ml CPT) and then analyzed. The method was validated for CPT-11 (5 to 25 000 ng/ml), SN-38 (5 to 2500 ng/ml) and SN-38G (2.5 to 500 ng/ml). This method enabled the determination of many samples within a relatively short time with easy sample preparation. It also had four advantages compared with conventional determination methods, i.e. automation of a complicated sample preparation, time-saving by the simultaneous determination of three compounds, the direct determination of SN-38G, and the small amount of plasma required for the determination. Copyright (C) 1999 Elsevier Science B.V.

L5 ANSWER 35 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 11
AN 1999086687 EMBASE
TI Effective Irinotecan (CPT-11)-containing liposomes: Intraliposomal conversion to the active metabolite SN-38.
AU Sadzuka Y.; Hirotsu S.; Hirota S.
CS Y. Sadzuka, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422-8526, Japan. sadzuka@ys7.u-shizuoka-ken.ac.jp
SO Japanese Journal of Cancer Research, (1999) 90/2 (226-232).
Refs: 19
ISSN: 0910-5050 CODEN: JJCREP
CY Japan
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Iriniotecan hydrochloride (CPT-11) is a prodrug of SN-38, which is an active metabolite with antitumor activity and side toxicity. The activities of CPT-11 and SN-38 depend on the closed lactone ring form of SN-38. We have examined the tissue distributions of the closed and open forms of CPT-11 and SN-38 in Lewis lung carcinoma-bearing mice after the administration of liposomal CPT-11 (S-Lip) and polyethyleneglycol (PEG)-modified S-Lip (S-PEG). The plasma concentrations of closed CPT-11 and SN-38 were increased by liposomalization, and their blood circulation was prolonged by the PEG modification. The concentrations of closed CPT-11 and SN-38 in tumors were elevated by both the liposomalization and PEG modification. The closed/total ratio of SN-38 in the tumors of the S-PEG group was greater than that of the CPT-11 solution (Sol) group. Thus, SN-38 was thought to be generated in intact liposomes containing CPT-11. The bile concentration of closed SN-38, which is responsible for CPT-11-induced intestinal disorder, was decreased by liposomalization. In an in vitro experiment, the SN-38/CPT-11 ratio in the tumor cells of the S-Lip group was found to be higher than that of the Sol group, and the ratio of the closed form of SN-38 was increased by the liposomalization. Laser scanning confocal microscopy showed the generation of SN-38 in the liposomal membrane after the incubation of S-Lip with
carboxylesterase . It is therefore considered that a part of CPT-11 is converted to SN-38 in the intact liposomes.

L5 ANSWER 36 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1999:226707 BIOSIS
DN PREV199900226707
TI CPT-11 is an inhibitor of acetylcholinesterase but can be activated to SN-38 by butyrylcholinesterases.
AU Potter, P. M. (1); Morton, C. L.; Wadkins, R. M.; Danks, M. K.
CS (1) Dep. Mol. Pharmacol., St. Jude Children's Res. Hosp., Memphis, TN 38105 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 210.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer

Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research
. ISSN: 0197-016X.
DT Conference
LA English

L5 ANSWER 37 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1999:226709 BIOSIS
DN PREV199900226709
TI Enhanced cytotoxicity to CPT-11 due to the bystander effect by cells expressing a secreted form of a rabbit liver ***carboxylesterase*** .
AU Wierdl, M.; Morton, C. L.; Danks, M. K.; Potter, P. M.
CS St. Jude Children's Res. Hosp., Memphis, TN 38105 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 210.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research
. ISSN: 0197-016X.
DT Conference
LA English

L5 ANSWER 38 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1999:184520 BIOSIS
DN PREV199900184520
TI Comparison of the efficiency of CPT-11 activation by a rabbit and a human ***carboxylesterase*** for use in enzyme/prodrug therapy.
AU Danks, M. K.; Morton, C. L.; Krull, E. J.; Cheshire, P. J.; Richmond, L. B.; Pawlik, C. A.; Houghton, P. J.; Potter, P. M.
CS St. Jude Child. Res. Hosp., Memphis, TN 38105 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 110.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research
. ISSN: 0197-016X.
DT Conference
LA English

L5 ANSWER 39 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1999:184521 BIOSIS
DN PREV199900184521
TI N-MYC-mediated overexpression of a CPT-11-activating enzyme in neuroblastoma cells.
AU Pawlik, C. A.; Iyengar, R. V.; Krull, E. J.; Harris, L. C.; Potter, P. M.; Danks, M. K.; Guichard, S. M.
CS St. Jude Child. Res. Hosp., Memphis, TN 38105 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 110.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999 American Association for Cancer Research
. ISSN: 0197-016X.
DT Conference
LA English

L5 ANSWER 40 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI.
B.V.DUPLICATE 12
AN 1998330138 EMBASE
TI Reversal of CPT-11 resistance of lung cancer cells by adenovirus- mediated gene transfer of the human ***carboxylesterase*** cDNA.
AU Kojima A.; Hackett N.R.; Crystal R.G.
CS R.G. Crystal, Div. of Pulmonary/Critical Care Med., New York Hospital-Cornell Med. Ctr., 520 East 70th Street, New York, NY 10021, United States. geneticmedicine@mail.med.cornell.edu
SO Cancer Research, (1 Oct 1998) 58/19 (4368-4374).
Refs: 54
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
LA English
SL English
AB To evaluate the concept that transfer of the human ***carboxylesterase*** (***CE***) gene will overcome the drug resistance of a solid tumor to CPT-11 (irinotecan), we used an adenovirus vector (AdCMV. ***CE***) carrying human ***CE*** cDNA to infect CPT-11-resistant A549 human adenocarcinoma cells (A549/CPT) in vitro and in vivo and evaluated cell growth over time. The A549/CPT cells, selected by stepwise and continuous exposure of parental A549 cells to CPT- 11 over 10 months, had a 6-fold resistance to CPT-11 and 42% ***CE*** activity in comparison with parental A549 cells. AdCMV. ***CE*** infection resulted in an increase in functional ***CE*** protein in resistant cells in vitro that was sufficient to convert CPT-11 to its active metabolite, SN-38, and effectively suppressed resistant cell growth in vitro in the presence of CPT-11. When AdCMV. ***CE*** was directly injected into established s.c. resistant A549-based tumors in nude mice receiving CPT-11, there was a 1.8-fold reduction in tumor size at day 20 compared to that of controls ($P < 0.05$). These observations suggest that adenovirus-mediated gene transfer of the human ***CE*** gene and concomitant administration of CPT-11 may have potential as a strategy for local control of acquired CPT-11 resistance of solid tumors.

L5 ANSWER 41 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI.
B.V.DUPLICATE 13
AN 1998275722 EMBASE
TI Cellular localization domains of a rabbit and a human ***carboxylesterase*** : Influence on irinotecan (CPT-11) metabolism by the rabbit enzyme.
AU Potter P.M.; Wolverton J.S.; Morton C.L.; Wierdl M.; Danks M.K.
CS M.K. Danks, Department of Molecular Pharmacology, St. Jude Children's Res. Hospital, 332 North Lauderdale, Memphis, TN 38105, United States. mary.danks@stjude.org
SO Cancer Research, (15 Aug 1998) 58/16 (3627-3632).
Refs: 30
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Enzyme activation of prodrugs to improve the therapeutic index of specific anticancer agents is an attractive alternative to current chemotherapy regimens. This study addresses the potential for activating irinotecan (CPT-11) with recombinant carboxylesterases (CEs). CEs are a ubiquitous class of enzymes thought to be involved in the detoxification of xenobiotics. Their primary amino acid sequence indicates that these proteins should be localized to the endoplasmic reticulum. By PCR-mediated mutagenesis of a rabbit liver and a human alveolar macrophage ***CE*** cDNA, expression in Cos7 cells, and subsequent immunohistochemical localization, we have determined that an 18-amino acid NH2-terminal hydrophobic signal peptide is responsible for the localization of these proteins to the endoplasmic reticulum. By similar approaches, we have demonstrated that the COOH-terminal amino acids HIEL prevent secretion of the proteins from the cell. Enzymatic activity was lost by removing the NH2-terminal domain; however, active enzyme could be detected in the culture media of cells expressing the COOH-terminally truncated proteins. Secretion of CEs lacking the six COOH-terminal amino acids could be prevented with brefeldin A, confirming that these truncated enzymes were processed and released from cells by endoplasmic reticulum- mediated exocytosis. Double-truncation mutant enzymes lacking both NH2- and COOH-terminal sequences demonstrated immunostaining patterns similar to those of the NH2-terminally truncated proteins and also lacked ***CE*** activity. In all cases, metabolism of the classic esterase substrate o-nitrophenyl acetate predicted the sensitivity of cells expressing the rabbit ***CE*** to the anticancer agent CPT-11. In addition, the secreted enzyme sensitized Cos7 cells to this drug, indicating that protein association with a lipid bilayer is not required for substrate metabolism.

L5 ANSWER 42 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI.
B.V.DUPLICATE 14
AN 1999000767 EMBASE
TI Conversion of the CPT-11 metabolite APC to SN-38 by rabbit liver ***carboxylesterase*** .
AU Guichard S.M.; Morton C.L.; Krull E.J.; Stewart C.F.; Danks M.K.; Potter P.M.
CS M.K. Danks, Department of Molecular Pharmacology, St. Jude Children's Res. Hospital, 332 North Lauderdale, Memphis, TN 38105, United States. mary.danks@stjude.org
SO Clinical Cancer Research, (1998) 4/12 (3089-3094).
Refs: 17
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
AB The anticancer drug CPT-11 (7-ethyl-[4(1-piperidino)1-piperidino]carbonyloxycamptothecin) is a water-soluble derivative of camptothecin. We report here the conversion of APC (7-ethyl-[4-N-(5-aminopentanoic acid)-l-piperidino] carbonyloxycamptothecin), an inactive metabolite of CPT-11, to SN-38 (7-ethyl-10-hydroxycamptothecin), the active metabolite of CPT-11, by a rabbit liver ***carboxylesterase*** . This reaction is not catalyzed by any known human enzyme. The formation of SN-38 from APC was characterized by an apparent K(m) of 37.9 .+-. 7.1 .mu.M and a V(max) of 16.9 .+-. 0.9 pmo/units/min. SN-38 was confirmed as a reaction product by high- performance liquid chromatography and mass spectrometry. A 24-h incubation of 10 .mu.M APC with 500 units/ml of rabbit ***carboxylesterase*** produced 4 .mu.M SN- 38. The product of this reaction inhibited the growth of U373 MG human glioblastoma cells in vitro. The IC50 for a 24-h exposure of U373 MG cells to APC in the presence of 50 units/ml of rabbit ***carboxylesterase*** was 0.27 .+-. 0.08 .mu.M, whereas APC alone demonstrated no inhibition of growth at concentrations up to 1 .mu.M. The IC50 of U373 MG cells transfected with the cDNA encoding the rabbit ***carboxylesterase*** (U373pIRESrabbit) and exposed to APC for 24 h was 0.8 .+-. 0.1 .mu.M APC, whereas the growth of cells transfected with vector control (U373pIRES) was unaffected by up to 1 .mu.M APC. Because APC is nontoxic to human cells, we are investigating the possibility of using APC/rabbit ***carboxylesterase*** in a prodrug/enzyme therapeutic approach.

L5 ANSWER 43 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 15
AN 1998263546 EMBASE
TI Pathophysiology and therapy of irinotecan-induced delayed-onset diarrhea in patients with advanced colorectal cancer: A prospective assessment.
AU Saliba F.; Hagipantelli R.; Misset J.-L.; Bastian G.; Vassal G.; Bonnay M.; Herait P.; Cote C.; Mahjoubi M.; Mignard D.; Cvitkovic E.
CS Dr. E. Cvitkovic, FSMSIT, Paul Brousse Hospital, 12 avenue Paul Vaillant Couturier, 94804 Villejuif, France. e.cvitkovic@cvitkovic.ac.pr
SO Journal of Clinical Oncology, (1998) 16/8 (2745-2751).
Refs: 40
ISSN: 0732-183X CODEN: JCONDN
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LA English
SL English
AB Purpose: Irinotecan (CPT-11), a camptothecin derivative, has shown efficacy against colorectal cancer. Delayed-onset diarrhea is its main limiting toxicity. The aim of this study was to determine the pathophysiology of CPT-11-induced delayed-onset diarrhea and assess the efficacy of combined antidiarrheal medication in a phase II, prospective, successive-cohorts, open study. Patients and Methods: Twenty-eight patients with advanced colorectal cancer refractory to fluorouracil (5-FU) therapy received CPT-11 350 mg/m2 every 3 weeks. The first cohort of 14 consecutive patients explored for the mechanism of diarrhea received acetorphan (a new enkephalinase inhibitor) 100 mg three times daily; the second 14-patient cohort received, in addition to acetorphan, loperamide 4 mg three times daily. Before treatment, and if late diarrhea occurred, patients underwent colon mucosal biopsies for CPT-11 and topoisomerase I levels; intestinal transit time; fecalogram; fat and protein excretion; alpha1-antitrypsin clearance; D-xylose test; blood levels for vasoactive intestinal polypeptide, glucagon, gastrin, somatostatin, prostaglandin E2, and ***carboxylesterase*** ; CPT-11/SN-38 and SN-38 glucuronide pharmacokinetics; and stool cultures. Results: Delayed-onset diarrhea occurred during the first three treatment cycles in 23 patients (82%). Electrolyte fecal measurements showed a negative or small osmotic gap in nine of nine patients and an increased alpha1-antitrypsin clearance in six of six patients. There were no modifications in stool cultures or hormonal dysfunction. Four of 11 patients (36%) with delayed-onset diarrhea in the first cohort responded to acetorphan, whereas nine of 10 patients (90%) responded to the combination of acetorphan and loperamide (P < .02). Conclusion: CPT-11-induced delayed-onset diarrhea is caused by a secretory mechanism with an exudative component. Early combined treatment with loperamide and acetorphan seems effective in controlling the diarrheal episodes.

L5 ANSWER 44 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 16
AN 1998199840 EMBASE
TI Isolation and partial characterization of a cDNA encoding a rabbit liver ***carboxylesterase*** that activates the prodrug irinotecan (CPT-11).
AU Potter P.M.; Pawlik C.A.; Morton C.L.; Naeve C.W.; Danks M.K.
CS P.M. Potter, Department of Molecular Pharmacology, St. Jude Children's Res. Hospital, 332 North Lauderdale Street, Memphis, TN 38105, United States. phil.potter@stjude.org
SO Cancer Research, (15 Jun 1998) 58/12 (2646-2651).
Refs: 27
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
AB We have isolated a cDNA encoding a rabbit ***carboxylesterase*** (***CE*** ; EC 3.1.1.1) that converts the camptothecin-derived prodrug irinotecan (CPT-11) to the potent topoisomerase I inhibitor 7-ethyl-10-hydroxycamptothecin. NH2- terminal amino acid sequencing of a purified rabbit ***CE*** allowed the design of redundant oligonucleotides to perform PCR from rabbit liver cDNA. DNA sequencing of the PCR product confirmed the identity of the clone, and after both 5' and 3' rapid amplification of cDNA ends, oligonucleotide primers were designed to amplify the entire cDNA. The 1698-bp open reading frame encoded a 565-amino acid protein containing the characteristic ***CE*** B-1 and B-2 motifs, a hydrophobic NH2-terminal leader sequence, and the COOH-terminal residues HIEL that are thought to be responsible for protein localization in the endoplasmic reticulum. Transient expression of the cDNA in COS-7 cells resulted in ***CE*** activity in cell extracts and increased the sensitivity of cells to CPT-11. Additionally, stable expression of the rabbit liver ***CE*** cDNA in the human glioma U-373 MG cell line resulted in a 56-fold decrease in the IC50 value for CPT-11, whereas the expression of a human alveolar macrophage cDNA encoding a highly homologous ***CE*** produced no change in drug sensitivity.

L5 ANSWER 45 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 17
AN 1998190281 EMBASE
TI Determinants of CPT-11 and SN-38 activities in human lung cancer cells.
AU Van Ark-Otte J.; Kedde M.A.; Van der Vijgh W.J.F.; Dingemans A.-M.C.; Jansen W.J.M.; Pinedo H.M.; Boven E.; Giaccone G.
CS G. Giaccone, Univ. Hospital Vrije Universiteit, Department of Medical Oncology, PO Box 7075, 1007 MB Amsterdam, Netherlands
SO British Journal of Cancer, (1998) 77/12 (2171-2176).
Refs: 37
ISSN: 0007-0920 CODEN: BJCAAI
CY United Kingdom
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
AB Irinotecan (CPT-11) is a semisynthetic camptothecin derivative with a broad spectrum of anti-tumour activity. ***Carboxylesterase*** (***CE***) catalyses the conversion of CPT-11 to SN-38 (7-ethyl-10-hydroxycamptothecin), the active form of CPT-11. The antiproliferative effects of CPT-11 and SN-38, ***CE*** -activity and topoisomerase I protein expression were investigated in five human small-cell lung cancer (SCLC) cell lines and four human non-small-cell lung cancer (NSCLC) cell lines. Antiproliferative activity, expressed as IC50 values, was determined using the MTT assay. CPT-11 was significantly more active in SCLC than in NSCLC cell lines (P = 0.0036), whereas no significant difference between histological types was observed with SN-38. A significant correlation ($r2 = 0.52$, P = 0.028) was observed between ***CE*** activity and chemosensitivity to CPT-11 but not to SN-38, and significantly higher ***CE*** activity was observed in SCLC compared with NSCLC cell lines (P = 0.025). Western blotting experiments showed topoisomerase I protein expressions within a factor of 2, and a granular nuclear staining was detectable in all cell lines by immunocytochemistry of cytospins. No correlation was observed between protein expression and sensitivity to CPT-11 or SN-38. Cellular and medium concentrations of CPT-11 and SN-38 were measured by high-performance liquid chromatography (HPLC) in one SCLC cell line with high ***CE*** activity and high sensitivity to CPT-11, and one NSCLC cell line with low sensitivity to CPT-11 and ***CE*** activity. Intracellular concentrations of CPT-11 and SN-38 were higher in the SCLC cell line, and this was associated with an increase in cellular uptake of CPT-11 compared with the medium, and an increased intracellular formation of SN-38. In conclusion, ***CE*** activity appears to be associated with higher sensitivity to CPT-11 in human lung cancer cell lines and may partly explain the difference in the in vitro sensitivity to CPT-11 between SCLC and NSCLC cells. The assessment of ***CE*** activity in clinical material of lung cancer patients undergoing treatment with CPT-11 may be warranted. However, other mechanisms may influence sensitivity to CPT-11, possibly including drug transport.

L5 ANSWER 46 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 18
AN 1998145451 EMBASE
TI In vivo human ***carboxylesterase*** cDNA gene transfer to activate the prodrug CPT-11 for local treatment of solid tumors.
AU Kojima A.; Hackett N.R.; Ohwada A.; Crystal R.G.
CS Dr. R.G. Crystal, Division of Pulmonary, Critical Care Medicine, New York Hospital-Cornell Med. Ctr., 520 East 70th Street, New York, NY 10021, United States
SO Journal of Clinical Investigation, (15 Apr 1998) 101/8 (1789-1796).
Refs: 46
ISSN: 0021-9738 CODEN: JCINAO
CY United States
DT Journal; Article
FS 016 Cancer
022 Human Genetics
037 Drug Literature Index
LA English
SL English
AB To evaluate the concept that in vivo transfer of the human ***carboxylesterase*** gene will confer sensitivity of a solid tumor to the prodrug CPT-11 (irinotecan), we constructed an adenovirus vector (AdCMV. ***CE***) carrying the human ***carboxylesterase*** gene driven by the cytomegalovirus (CMV) promoter, infected A549 human lung adenocarcinoma cells in vitro and in vivo, and evaluated cell growth over time. AdCMV. ***CE*** produced a functional ***carboxylesterase*** protein in A549 cells in vitro and in vivo as evidenced by ability of lysates from the infected cells to convert CPT-11 to its active metabolite SN-38. The AdCMV. ***CE*** vector effectively suppressed A549 cell growth in vitro in the presence of CPT-11. Cell mixing studies demonstrated that when as few as 10% of cells expressed the human ***carboxylesterase*** gene, there was bystander growth suppression in the presence of CPT-11. Consistent with these in vitro observations, when AdCMV. ***CE*** was directly injected into established subcutaneous A549 tumors in nude mice receiving CPT-11, there was 35% reduction in tumor size at day 27 compared to controls, and a 41% reduction at day 34 (P < 0.01, both comparisons to controls). Similar observations were made with the cell line H157 and HeLa. These observations suggest that local gene transfer of the human ***carboxylesterase*** gene and concomitant local administration of CPT-11 may have potential as a strategy for control of the growth of solid tumors.

L5 ANSWER 47 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998376263 EMBASE
TI Pharmacology of irinotecan.
AU Robert J.; Rivory L.
CS J. Robert, Institut Bergonie, Universite Victor Segalen Bordeaux 2, 180

rue de Saint-Genes, 33076 Bordeaux Cedex, France
SO Drugs of Today, (1998) 34/9 (777-803).
Refs: 187
ISSN: 0025-7656 CODEN: MDACAP
CY Spain
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Irinotecan (CPT-11) is a semisynthetic derivative of camptothecin, an alkaloid extracted from the Chinese plant Camptotheca acuminata. It bears a bis-piperidine moiety and was selected for its water solubility and promising preclinical antitumor activity in in vitro and in vivo models. The target of drugs of the camptothecin family is DNA topoisomerase I, a nuclear enzyme involved in the relaxation of the DNA double helix required for replication and transcription activities. They stabilize the enzyme-DNA complex and prevent the religation of the single-strand breaks created by the enzyme, which are converted to double-strand breaks upon the collision with a replication fork during the S-phase. Resistance to irinotecan appears not to be mediated by P-glycoprotein, but by qualitative and/or quantitative alterations of its target, topoisomerase I, or by alterations occurring downstream of this interaction. As with all camptothecin derivatives, irinotecan contains a lactone ring that can be spontaneously and reversibly hydrolyzed to a carboxylate open ring form, which predominates at neutral and alkaline pH and is inactive on topoisomerase I-DNA complexes. Irinotecan is, in fact, much less active than its metabolite SN-38 and is generally considered as a prodrug of this compound. The ***carboxylesterase*** which carries out this conversion is preferentially active on the lactone form of irinotecan and directly generates the lactone form of SN-38, which may explain the superiority of irinotecan overs SN-38 in vivo. Further metabolism of SN-38 to a beta-glucuronide conjugate is a major pathway of detoxification and plays an important role in determining the irinotecan toxicity in the clinical setting. Other metabolic pathways of irinotecan involve oxidations occurring on the bis-piperidine rings, which are carried out by cytochrome P450. Irinotecan has shown an important activity in advanced and metastatic colorectal carcinoma and is now used for this indication in several countries, with two different recommended schedules: weekly administration of 125 mg/m2 with a 2-week drug-free interval every 4 administrations or 3- weekly administration of 350 mg/m2, a dose that can be increased to 500 mg/m2 with the support of antidiarrhetics. Other possible indications of irinotecan include lung and cervix cancer, which are presently under investigation. The dose-limiting toxicity of irinotecan is mainly diarrhea, which occurs 7-10 days after treatment and can be life-threatening when associated with neutropenia, another frequent side effect. High-dose loperamide has shown good efficacy for treating this diarrhea and has allowed an increase in irinotecan doses tolerated by patients. The pharmacokinetics of irinotecan are characterized by a 2- or 3-compartment decay, with a terminal half-life of about 10 h, a total volume of distribution of 150 l/m2 and a total plasma clearance of 15 l/h/m2. SN-38 AUC is only a small fraction of that of irinotecan (2-4%) and SN-38 is eliminated from plasma with a half-life of about 2 h. SN-38 glucuronide is present in plasma at higher concentrations that SN-38 and is eliminated at the same time rate. APC, produced by the action of cytochrome P450, isoenzyme 3A4, is present in plasma at concentrations close to those of irinotecan itself. Only a small fraction of irinotecan and its metabolites is eliminated in urine and a higher proportion in the bile, with an enterohepatic cycle of SN-38 glucuronide and SN-38. Significant relationships have been established between the AUCs of both irinotecan and SN-38 and hematological and intestinal toxicities, suggesting a potential use for monitoring of this drug.

L5 ANSWER 48 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 19
AN 1998231380 EMBASE
TI Identification of a new metabolite of CPT-11 (irinotecan): Pharmacological properties and activation to SN-38.
AU Dodds H.M.; Haaz M.-C.; Riou J.-F.; Robert J.; Rivory L.P.
CS Dr. J. Robert, Institut Bergonie, 180 rue de Saint-Genes, 33076 Bordeaux-Cedex, France
SO Journal of Pharmacology and Experimental Therapeutics, (1998) 286/1 (578-583).
Refs: 15
ISSN: 0022-3565 CODEN: JPETAB
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Irinotecan, or CPT-11 (7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecine), is a water-soluble derivative of camptothecine with promising activity against several types of malignancies. In addition to 7-ethyl-10-hydroxycamptothecine (SN-38), its active metabolite, we were able to identify several metabolites in the plasma of patients treated with this drug, especially an oxidative metabolite, 7- ethyl-10[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxy-camptothecine. During our study of the biosynthesis of 7-ethyl-10[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxy-camptothecine from CPT-11 by human liver microsomes, we were able to detect another quantitatively important polar metabolite, which was also present in the plasma and urine of patients treated with CPT-11. On the basis of preliminary experiments, the structure of this compound was postulated to be 7-ethyl-10(4-amino-1- piperidino)carbonyloxycamptothecine , and this structure was synthesized by Rhone-Poulenc Rorer. Urine samples and human liver microsomal extracts were studied by high-performance liquid chromatography/atmospheric pressure chemical ionization/tandem mass spectrometry to identify its structure formally. The identification of the metabolite was supported by identical retention time, mass-to-charge ratio and tandem mass spectrometry fragmentation as a synthetic standard. Like irinotecan, 7-ethyl-10-(4-amino- 1-piperidino) carbonyloxycamptothecine was a weak inhibitor of cell growth of P388 cells in culture (IC50 = 3.4 .mu.g/ml vs. 2.8 .mu.g/ml for irinotecan and 0.001 .mu.g/ml for SN-38). It was also a poor inducer of topoisomerase I- DNA cleavable complexes (100-fold less potent than SN-38). However, unlike 7- ethyl-10[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxy-camptothecine, this new metabolite could be hydrolyzed to SN-38 by human liver microsomes and purified human liver ***carboxylesterase*** , though to a lesser extent than irinotecan. This compound can therefore contribute to the activity and toxicity profile of irinotecan in vivo.

L5 ANSWER 49 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998088245 EMBASE
TI Altered irinotecan and SN-38 disposition after intravenous and oral administration of irinotecan in mice bearing human neuroblastoma xenografts.
AU Zamboni W.C.; Houghton P.J.; Thompson J.; Cheshire P.J.; Hanna S.K.; Richmond L.B.; Lou X.; Stewart C.F.
CS C.F. Stewart, Dept. of Pharmaceutical Sciences, St. Jude Children's Res. Hospital, 332 North Lauderdale, Memphis, TN 38105, United States
SO Clinical Cancer Research, (1998) 4/2 (455-462).
Refs: 34
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
016 Cancer
037 Drug Literature Index
LA English
SL English
AB The antitumor activity of irinotecan in vitro primarily results from its hydrolysis by ***carboxylesterase*** to the active metabolite SN-38. The present study was conducted to evaluate the effect of human neuroblastoma xenografts on irinotecan and SN-38 disposition after i.v. and oral irinotecan administration. Non-tumor-bearing mice and mice bearing three different human neuroblastoma xenograft lines (NB1691, NB1643, and NBEB) were given irinotecan (10 mg/kg) by short i.v. injection into the tail vein or by oral gavage. Serial plasma samples were obtained, processed to isolate irinotecan and SN-38 lactone, and assayed with a sensitive and specific high-performance liquid chromatography assay. Noncompartmental and compartmental pharmacokinetic analyses were performed. A four-compartment model was used for analysis of irinotecan and SN-38 concentration-time data after i.v. administration. The presence of tumor increased irinotecan systemic exposure (1.2-3.8 fold; $P < 0.05$) after i.v. and oral administration in mice bearing neuroblastoma xenografts compared to non-tumor-bearing mice. Moreover, SN-38 systemic exposures were higher (1.3-3.8-fold; $P < 0.05$) in mice bearing human neuroblastoma xenografts as compared to non-tumor-bearing mice, with the greatest effect observed after oral administration of irinotecan. A schematic model is presented to provide a mechanistic basis for our observations. These results emphasize the need to perform preclinical pharmacokinetic studies to evaluate the influence of tumor on drug disposition.

L5 ANSWER 50 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1998:196739 BIOSIS
DN PREV199800196739
TI Isolation and characterization of a cDNA encoding a rabbit ***carboxylesterase*** that converts CPT-11 to SN-38.
AU Potter, P. M.; Pawlik, C. A.; Morton, C. M.; Danks, M. K.
CS St. Jude Child. Res. Hosp., Memphis, TN 38105 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 421.
Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998 American Association for Cancer Research
. ISSN: 0197-016X.
DT Conference
LA English

L5 ANSWER 51 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1998:196738 BIOSIS
DN PREV199800196738
TI Epitope-tagged rabbit liver ***carboxylesterase*** confers sensitivity to CPT-11 and localizes to the endoplasmic reticulum.
AU Wolverton, J. S.; Potter, P. M.; Whipple, D. O.; Morton, C. L.; Danks, M. K.
CS St. Jude Child. Res. Hosp., Memphis, TN 38105 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 421.
Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998 American Association for Cancer Research
. ISSN: 0197-016X.

DT Conference
LA English

L5 ANSWER 52 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998065023 EMBASE
TI Synthesis of a new class of camptothecin derivatives, the long-chain fatty acid esters of 10-hydroxycamptothecin, as a potent prodrug candidate, and their in vitro metabolic conversion by carboxylesterases.
AU Takayama H.; Watanabe A.; Hosokawa M.; Chiba K.; Satoh T.; Aimi N.
CS N. Aimi, Faculty of Pharmaceuitcal Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263, Japan
SO Bioorganic and Medicinal Chemistry Letters, (3 Mar 1998) 8/5 (415-418).
Refs: 9
ISSN: 0960-894X CODEN: BMCLE8
PUI S 0960-894X(98)00039-0
CY United Kingdom
DT Journal; Article
FS 037 Drug Literature Index
LA English
SL English
AB Five (20S)-10-hydroxycamptothecin derivatives carrying the long-chain fatty acid eaters were prepared for the development of a new class of prodrug-type agents. In vitro experiments using three kinds of purified ***carboxylesterase*** isozymes from the liver microsomes of rat, pig, and human demonstrated that these derivatives were efficiently metabolized by enzymes compared with CPT-11.

L5 ANSWER 53 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 20
AN 1998029760 EMBASE
TI CPT-11 sensitivity in relation to the expression of P170-glycoprotein and multidrug resistance-associated protein.
AU Jansen W.J.M.; Hulscher T.M.; Van Ark-Otte J.; Giaccone G.; Pinedo H.M.; Boven E.
CS E. Boven, Department of Medical Oncology, Academic Hospital Vrije Universiteit, De Boelelaan 1117, 1081 HV Amsterdam, Netherlands
SO British Journal of Cancer, (1998) 77/3 (359-365).
Refs: 33
ISSN: 0007-0920 CODEN: BJCAAI
CY United Kingdom
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
AB The relevance of P170-glycoprotein (P-gp) and multidrug resistance-associated protein (MRP) for the sensitivity to CPT-11 was investigated in human malignant cell lines as well as in human tumour xenografts. In vitro, the P-gp-positive sublines BRO/mdr1.1 (transfected with MDR1) and 2780(AD) were slightly cross-resistant against ***carboxylesterase*** -activated CPT-11. Cross-resistance against SN-38 was present in 2780(AD) cells, but not in BRO/mdr1.1 cells. The P-gp modulators BIBW22BS, verapamil and dexniguldipine partly reversed the resistance against CPT-11 in the P-gp-positive sublines. BIBW22BS was the most effective modulator in the reversal of the resistance against ***carboxylesterase*** -activated CPT-11 as well as against SN-38 in the 2780(AD) subline. In contrast to doxorubicin and vincristine, the BRO/mdr1.1 xenografts were at least as sensitive to CPT-11 as the BRO xenografts. The 2780(AD) xenografts were slightly less sensitive than the parent tumours, but there was no difference in topoisomerase I DNA unwinding activity. Therefore, the high retention of the multidrug resistant phenotype of 2780(AD) cells in vivo may be the cause of the low cross-resistance against CPT-11. The MRP-positive subline GLC4/ADR was cross-resistant against ***carboxylesterase*** -activated CPT-11 and SN-38. GLC4/ADR cells, however, demonstrated a twofold lower topoisomerase I activity than GLC4 cells. Cross-resistance against the camptothecin derivatives was not apparent in the MRP-transfected subline of SW1573/S1. In conclusion, P-gp-positive cells show a low cross-resistance against CPT-11/SN38, which is only apparent with high P-gp expression in vivo. MRP does not seem to play a role in the sensitivity to CPT-11.

L5 ANSWER 54 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998149319 EMBASE
TI Preclinical development of camptothecin derivatives and clinical trials in pediatric oncology.
AU Vassal G.; Pondarre C.; Boland I.; Cappelli C.; Santos A.; Thomas C.; Lucchi E.; Imadalou K.; Pein F.; Morizet J.; Gouyette A.
CS G. Vassal, Department of Pediatric Oncology, Institut Gustave-Roussy, rue Camille Desmoulins, 94805 Villejuif, France
SO Biochimie, (1998) 80/3 (271-280).
Refs: 66
ISSN: 0300-9084 CODEN: BICMBE
CY France
DT Journal; General Review
FS 007 Pediatrics and Pediatric Surgery
016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Although the prognosis of childhood cancers has dramatically improved over the last three decades, new active drugs are needed. Camptothecins represent a very attractive new class of anticancer drugs to develop in paediatric oncology. The preclinical and clinical development of two of these DNA-topoisomerase I inhibitors, ie topotecan and irinotecan, is ongoing in paediatric malignancies. Here we review the currently available results of this evaluation. Topotecan proved to be active against several paediatric tumour xenografts. In paediatric phase I studies exploring several administration schedules, myelosuppression was dose-limiting. The preliminary results of topotecan evaluation in phase II study showed antitumour activity in neuroblastoma (response rate: 15% at relapse and 37% in newly diagnosed patients with disseminated disease) and in metastatic rhabdomyosarcoma (40% in untreated patients). Topotecan-containing drug combinations are currently investigated. Irinotecan displayed a broad spectrum of activity in paediatric solid tumour xenografts, including rhabdomyosarcoma, neuroblastoma, peripheral primitive neuroectodermal tumour, medulloblastoma, ependymoma, malignant glioma and juvenile colon cancer. For several of these histology types, tumour-free survivors have been observed among animals bearing an advanced-stage tumour at time of treatment. The clinical evaluation of irinotecan in children is ongoing. Iinotecan undergoes a complex in vivo biotransformation involving several enzyme systems, such as ***carboxylesterase*** , UDPGT and cytochrome P450, in children as well as in adults. Preclinical studies of both drugs have shown that their activity was schedule-dependent. The optimal schedule of administration is an issue that needs to be addressed in children. In conclusion, the preliminary results of the paediatric evaluation of camptothecin derivatives show very encouraging results in childhood malignancies. The potential place of camptothecins in the treatment of paediatric malignant tumours is discussed.

L5 ANSWER 55 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1998:194427 BIOSIS
DN PREV199800194427
TI Overexpression of a rabbit liver ***carboxylesterase*** sensitizes Rh30 human tumor cells to CPT-11.
AU Pawlik, C. A.; Morton, C. L.; Danks, M. K.; Potter, P. M.
CS St. Jude Children's Res. Hosp., Memphis, TN 38105 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 81.
Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998 American Association for Cancer Research
. ISSN: 0197-016X.
DT Conference
LA English

L5 ANSWER 56 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998384706 EMBASE
TI Alternative dosing schedules irinotecan.
AU Rothenberg M.L.; Kuhn J.G.; Schaaf L.J.; Drengler R.L.; Hammond L.; Miller L.L.; Petit R.G.; Rowinsky E.K.; Von Hoff D.D.
CS Dr. M.L. Rothenberg, Division of Medical Oncology, Vanderbilt University Medical Center, 1956 Vanderbilt Clinic, Nashville, TN 37232, United States
SO ONCOLOGY, (1998) 12/8 SUPPL. (68-71).
Refs: 9
ISSN: 0890-9091 CODEN: OCLGE
CY United States
DT Journal; Conference Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Most of the clinical experience with irinotecan (CPT-II [Camptosar]) has been with either a weekly or an every-3-week schedule. Recent phase I trials have explored new routes and schedules of administration. One approach attempts to maximize dose frequency and intensity by giving irinotecan every 2 weeks. A phase I trial of this approach is now complete and has led to a phase II trial in patients with recurrent colorectal cancer. Data suggest that smaller doses of a topoisomerase I inhibitor administered repeatedly may result in greater antitumor activity than larger doses administered intermittently. A phase I trial has been performed in adults in which irinotecan was administered daily for 5 consecutive days, followed by 2 days off, for 2 weeks out of 3. Similar trials are under way in children. Oral administration, another strategy that has undergone phase I testing, has several theoretical advantages: (1) The acidic pH of the stomach favors maintenance of irinotecan in the active lactone ring form. (2) Irinotecan is more rapidly and extensively converted to SN-38 by tissue carboxylesterases found in high concentrations in the gut and liver. (3) Low doses can be delivered over a protracted period. (4) The oral route enhances patient convenience. These alternative dosing schedules may facilitate integration of irinotecan into combination chemotherapy and combined-modality treatment regimens.

L5 ANSWER 57 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998384700 EMBASE
TI Pharmacology of irinotecan.
AU Kuhn J.G.
CS Prof. J.G. Kuhn, Department of Medicine, Univ. of Texas Hlth. Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284-6220, United States
SO ONCOLOGY, (1998) 12/8 SUPPL. (39-42).
Refs: 16

ISSN: 0890-9091 CODEN: OCLGE
CY United States
DT Journal; Conference Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Irinotecan (CPT-11 [Camptosar]), a semisynthetic derivative of the plant alkaloid camptothecin, is bioactivated by carboxylesterases (EC3.1.1-) to the topoisomerase I inhibitor SN-38, a minor metabolite. Bioactivation of intravenously administered irinotecan by carboxylesterases occurs predominantly in the liver. Two human ***carboxylesterase*** isoforms responsible for SN-38 formation have been characterized. At relevant hepatic irinotecan concentrations up to 12 .mu.g/mL, a low-Km isoform is responsible for irinotecan bioactivation. High concentrations of drugs commonly coadministered with irinotecan do not inhibit ***carboxylesterase*** activity. Intestinal carboxylesterases can also generate SN-38, followed by subsequent oral absorption. A second major polar metabolite of irinotecan, aminopentanecarboxylic acid (APC), is the product of CYP3A4-mediated oxidation of the terminal piperidine ring. APC is 100-fold less active than SN-38 as a topoisomerase I inhibitor and is a relatively weak inhibitor of acetylcholinesterase. SN-38 is eliminated mainly through conjugation by hepatic uridine glucuronosylansferase (UGT*1.1), the same isoezyme responsible for glucuronidation of bilirubin. Grade 4 irinotecan-related toxicity (ie, neutropenia, diarrhea) has recently been reported in two patients with deficient UGT*1.1 activity. SN-38 glucuronide (SN-38G), which has only 1/100th the antitumor activity of SN-38, is actively secreted into the bile by a canalicular multispecific organic anion transporter. Deconjugation of SN-38G to SN-38 by beta-glucuronidase produced by the intestinal flora may contribute to enterohepatic recirculation of SN-38 and delayed intestinal toxicity.

L5 ANSWER 58 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 21
AN 1998018429 EMBASE
TI Overexpression of a rabbit liver ***carboxylesterase*** sensitizes human tumor cells to CPT-11.
AU Danks M.K.; Morton C.L.; Pawlik C.A.; Potter P.M.
CS P.M. Potter, Department of Molecular Pharmacology, St. Jude Children's Res. Hospital, 332 North Lauderdale, Memphis, TN 38105, United States. phil.potter@stjude.org
SO Cancer Research, (1998) 58/1 (20-22).
Refs: 18
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
AB CPT-11 [7-ethyl-10-[4-(1-piperidino)-1- piperidino]carbonyloxycamptothecin] is a prodrug that is converted to the active metabolite SN-38 by carboxylesterases. In its active form, the drug inhibits topoisomerase I, causes DNA damage, and induces apoptosis. Data in this study show metabolism of CPT-11 to SN-38 (7-ethyl-10- hydroxycamptothecin) by a rabbit liver ***carboxylesterase*** in vitro and growth- inhibitory activity of the products of the reaction. Additionally, stable expression of the cDNA encoding this protein in Rh30 human rhabdomyosarcoma cells increased the sensitivity of the cells to CPT-11 8.1-fold. We propose that this prodrug/enzyme combination can be exploited therapeutically in a manner analogous to approaches currently under investigation with the combinations of ganciclovir/herpes simplex virus thymidine kinase and 5-fluorocytosine/cytosine deaminase.

L5 ANSWER 59 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998344491 EMBASE
TI The clinical pharmacology of topoisomerase I inhibitors.
AU Abang A.M.
CS Dr. A.M. Abang, Univ. of Oklahoma Health Sci. Ctr., College of Pharmacy, PO Box 26901, Oklahoma City, OK 73190, United States
SO Seminars in Hematology, (1998) 35/3 SUPPL. 4 (13-21).
Refs: 39
ISSN: 0037-1963 CODEN: SEHEA3
CY United States
DT Journal; General Review
FS 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The Chinese tree Camptotheca acuminata, or Xi Shu, brings us a unique class of chemotherapeutic agents known as the camptothecins. Because the parent compound exhibited excessive toxicity and poor aqueous solubility, synthetic and semisynthetic analogs were developed. These compounds contain a lactone ring that is necessary for activity and is easily hydrolyzed into the less active hydroxy caborxylic acid. Irinotecan, a semisynthetic analog is a prodrug that is cleaved by a ***carboxylesterase*** -converting enzyme to form the biologically active metabolite SN-38. The half-lives of irinotecan and SN-38 are relatively long, and both are commonly found in the lactone form. Topotecan differs from irinotecan in that it is found predominately in the inactive carboxylate form at neural pH, but can be maintained in the lactone form at a lower pH. In phase I clinical trials, the antitumor activity of topotecan has been impressive. In vitro and in vivo studies have shown that combinations between topotecan and 5-fluorouracil or cisplatin have synergistic antitumor effects compared with topotecan alone. Two relatively new agents, 9-aminocamptothecin and GG211, have produced promising results against a variety of tumors.

L5 ANSWER 60 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 22
AN 97375007 EMBASE
DN 1997375007
TI Intravenous administration of irinotecan elevates the blood .beta.-glucuronidase activity in rats.
AU Kaneda N.; Kurita A.; Hosokawa Y.; Yokokura T.; Awazu S.
CS N. Kaneda, Yakult Central Institute, Microbiological Research, 1796 Yao, Kunitachi, Tokyo 186, Japan
SO Cancer Research, (1997) 57/23 (5305-5308).
Refs: 25
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
AB 7-Ethyl-10-hydroxycamptothecin (SN-38) is the active metabolite of an anticancer drug, irinotecan (CPT-11). Severe late diarrhea is the dose-limiting toxic effect of CPT-11. This diarrhea has been examined regarding biliary excretion and deconjugation of SN-38 glucuronide by the enzyme .beta.- glucuronidase (.beta.-GL) in intestinal microflora. Prompted by the enzymological and structural similarity of CPT-11 to organophosphorus and carbamate insecticides, we studied the effect of CPT-11 on blood .beta.-GL activity in rats. The i.v. injection of CPT-11 in rats significantly elevated their plasma .beta.-GL activity (with phenolphthalein glucuronide as a substrate) at doses of 10 and 40 mg/kg, with peak activity observed 2-3 h after administration. SN-38 lactone and carboxylate had no effect on the plasma .beta.- GL level. The enhancement of the activity was also observed in serum using SN-38 glucuronide as a substrate. The serum .beta.-GL levels showed a close correlation between these substrates. The enhancement of plasma (serum) .beta.- GL activity is suggested to be a result of the release of .beta.-GL, from liver microsomes. Serum and microsomal ***carboxylesterase*** were not significantly affected by CPT-11 administration.

L5 ANSWER 61 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 23
AN 97320512 EMBASE
DN 1997320512
TI Bioactivation of the anticancer agent CPT-11 to SN-38 by human hepatic microsomal carboxylesterases and the in vitro assessment of potential drug interactions.
AU Slatter J.G.; Su P.; Sams J.P.; Schaaf L.J.; Wienkers L.C.
CS Dr. J.G. Slatter, Drug Metabolism Research, Pharmacia and Upjohn Co., 301 Henrietta St., Kalamazoo, MI 49007, United States. john.g.slatter@am.pnu.com
SO Drug Metabolism and Disposition, (1997) 25/10 (1157-1164).
Refs: 41
ISSN: 0090-9556 CODEN: DMDSAI
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Human hepatic microsomes were used to investigate the ***carboxylesterase*** - mediated bioactivation of CPT-11 to the active metabolite, SN-38. SN-38 formation velocity was determined by HPLC over a concentration range of 0.25- 200 .mu.M CPT-11. Biphasic Eadie Hofstee plots were observed in seven donors, suggesting that two isoforms catalyzed the reaction. Analysis by nonlinear least squares regression gave K(M) estimates of 129-164 .mu.M with a V(max) of 5.3-17 pmol/mg/min for the low affinity isoform. The high affinity isoform had K(M) estimates of 1.4-3.9 .mu.M with V(max) of 1.2-2.6 pmol/mg/min. The low K(M) ***carboxylesterase*** may be the main contributor to SN-38 formation at clinically relevant hepatic concentrations of CPT-11. Using standard incubation conditions, the effects of potential inhibitors of ***carboxylesterase*** -mediated CPT-11 hydrolysis were evaluated at concentrations .ltoreq. 21 .mu.M. Positive controls bis-nitrophenylphosphate (BNPP) and physostigmine decreased CPT-11 hydrolysis to 1.3-3.3% and 23% of control values respectively. Caffeine acetylsalicylic acid coumarin, cisplatin, ethanol dexamethasone, 5-fluorouracil, loperamide, and prochlorperazine had no statistically significant effect on CPT-11 hydrolysis. Small de- creases were observed with metoclopramide (91% of control), acetaminophen (93% of control), probenecid (87% of control), and fluoride (91% of control). Of the compounds tested above, based on these in vitro data, only the potent inhibitors of ***carboxylesterase*** (BNPP, physostigmine) have the potential to inhibit CPT-11 bioactivation if administered concurrently. The ***carboxylesterase*** -mediated hydrolysis of .alpha.-naphthyl acetate (.alpha.-NA) was used to determine whether CPT-11 was an inhibitor

of hydrolysis of high turnover substrates of carboxylesterases. Inhibition of .alpha.-NA hydrolysis by CPT-11 was determined relative to positive controls BNPP and NaF. Incubation with microsomes pretreated with CPT-11 (8-440 .mu.M) decreased .alpha.-naphthol formation to approximately 80% of control at .alpha.-NA concentrations of 50-800 .mu.M. The inhibitors BNPP (360 .mu.M) and NaF (500 .mu.M) inhibited .alpha.-naphthol formation to 9-10% of control and to 14-20% of control, respectively. Therefore, CPT-11-sensitive ***carboxylesterase*** isoforms may account for only 20% of total .alpha.- NA hydrolases. Thus, CPT-11 is unlikely to significantly inhibit high turnover, nonselective substrates of carboxylesterases.

L5 ANSWER 62 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 24
AN 97070447 EMBASE
DN 1997070447
TI CPT-11 in human colon-cancer cell lines and xenograft: Characterization of cellular sensitivity determinants.
AU Jansen W.J.M.; Zwart B.; Hulscher S.T.M.; Giaccone G.; Pinedo H.M.; Boven E.
CS E. Boven, Academic Hospital Vrije Universiteit, Department of Medical Oncology, De Boelelaan 1117, 1081 HV Amsterdam, Netherlands. e.boven.oncol@med.vu.nl
SO International Journal of Cancer, (1997) 70/3 (335-340).
Refs: 27
ISSN: 0020-7136 CODEN: IJCNAW
CY United States
DT Journal; Article
FS 016 Cancer
048 Gastroenterology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB CPT-11, a new semisynthetic derivative of camptothecin, is active in a number of tumor types in the clinic, including colon cancer. CPT-11 is a drug that is converted into the active metabolite SN-38 by a ***carboxylesterase*** . Experiments were performed to obtain more insight in the cellular characteristics in 5 unselected human colon-cancer cell lines that account for the differential sensitivity to CPT-11 and SN-38. In vitro, the sensitivity to CPT-11 and SN-38 was highest in LS174T and COLO 320 cells, intermediate in SW1398 cells and lowest in COLO 205 and WiDr cells. SN-38 was 130 to 570 times more active than CPT-11. CPT-11 induced complete remissions in 6 out of 12 COLO 320 tumors grown as subcutaneous xenografts, but was not effective in WiDr tumors. The cellular ***carboxylesterase*** activity did not relate to the sensitivity to CPT-11. The enzyme activity was higher in normal mouse tissues, i.e., serum and liver, than in COLO 320 or WiDr xenografts, indicating that tumor ***carboxylesterase*** is of minor importance for CPT-11 efficacy. The topoisomerase-I mRNA expression in tumor cells was not predictive of the antiproliferative effects of CPT-11 or SN-38. We observed a positive relationship between the DNA topoisomerase-I activity and the cellular sensitivity to ***carboxylesterase*** -activated CPT-11 ($r = 0.75$, $p < 0.1$) as well as to SN-38 ($r = 0.89$, $p < 0.05$). The higher topoisomerase-I activity in COLO 320 cells and tumors when compared with that in WiDr cells and tumors reflected the differences in sensitivity to the drug(s). In conclusion, the DNA topoisomerase-I activity was the best determinant for CPT-11/SN-38 sensitivity in this panel of unselected human colon-cancer cell lines.

L5 ANSWER 63 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 25
AN 97245423 EMBASE
DN 1997245423
TI The transformation of irinotecan (CPT-11) to its active metabolite SN-38 by human liver microsomes. Differential hydrolysis for the lactone and carboxylate forms.
AU Haaz M.-C.; Rivory L.P.; Riche C.; Robert J.
CS J. Robert, Institut Bergonie, University of Bordeaux II, 180 rue de Saint-Genes, F-33076 Bordeaux-Cedex, France
SO Naunyn-Schmiedeberg's Archives of Pharmacology, (1997) 356/2 (257-262).
Refs: 21
ISSN: 0028-1298 CODEN: NSAPCC
CY Germany
DT Journal; Article
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB Irinotecan (CPT-11) is a new camptothecine derivative presently in development for the treatment of several advanced malignancies. It is converted in vivo to a highly potent metabolite, SN-38, by carboxylesterases. All camptothecine derivatives undergo lactonolysis in a pH-dependent reversible manner, generating inactive carboxylate forms. We have investigated in vitro the kinetics of transformation of CPT-11 to SN-38 by human liver microsomes originating from several donors. Microsomes from seven livers were studied individually or as a pooled preparation. CPT-11, either in its lactone or its carboxylate form, was added at a range of concentrations. The SN-38 formed was measured by HPLC with fluorometric detection. In the deacylation-limited ***carboxylesterase*** reaction, the linear steady-state kinetics between 10 and 60 min were determined. At all concentrations of CPT-11, the steady-state velocity of SN-38 formation as well as the intercept concentrations of SN-38 were about 2-fold higher when the substrate was under the lactone form than under the carboxylate form. We estimated the values (.+-.SD) of K'(m) and V(max) to be 23.3.+-.5.3 .mu.M and 1.43.+-.0.15 pmol/min/mg for the lactone and 48.9.+-.5.5 .mu.M and 1.09.+-.0.06 pmol/min/mg for the carboxylate form of CPT-11, respectively. We conclude that the greater rate of conversion of CPT-11 lactone may contribute to the plasma predominance of SN-38 lactone observed in vivo. The inter-individual variation of SN-38 formation was relatively high (ratio of 4 between extreme values) but no large age- or gender-related differences were seen. The effect of twelve drugs of different therapeutic classes (antibiotics, antiemetics, antineoplastics, antidiarrhoeics, analgesics), which could be administered in association with irinotecan in the clinical setting, was evaluated in this system (drug concentration: 100 .mu.M; CPT-11 lactone concentration: 10 .mu.M). Loperamide and ciprofloxacine where the only drugs exerting a weak inhibition of CPT-11 conversion to SN-38.

L5 ANSWER 64 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 97260818 EMBASE
DN 1997260818
TI Cytotoxic agent. Irinotecan.
SO Manufacturing Chemist, (1997) 68/8 (37).
Refs: 0
ISSN: 0262-4230 CODEN: MCHMDI
CY United Kingdom
DT Journal; Note
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LA English

L5 ANSWER 65 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 26
AN 96250526 EMBASE
DN 1996250526
TI Involvement of .beta.-glucuronidase in intestinal microflora in the intestinal toxicity of the antitumor camptothecin derivative irinotecan hydrochloride (CPT-11) in rats.
AU Takasuna K.; Hagiwara T.; Hirohashi M.; Kato M.; Nomura M.; Nagai E.; Yokoi T.; Kamataki T.
CS Drug Safety Research Laboratory, Daiichi Pharmaceutical Co., Ltd., 16-13 Kitakasai 1-chome,Edogawa-ku, Tokyo 134, Japan
SO Cancer Research, (1996) 56/16 (3752-3757).
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB Irinotecan hydrochloride (CPT-11), an antitumor camptothecin derivative, causes severe forms of diarrhea clinically. We characterized CPT-11-induced diarrhea histologically and enzymologically and assessed the relationships between intestinal toxicity and the activity of the enzymes that play a key role in the major metabolic pathway of CPT-11 in rats. CPT- 11 (60 mg/kg i.v. for 4 days) induced intestinal toxicity characterized by severe chronic diarrhea, loss of body weight, and anorexia. Histological damage was most severe in the cecum. The segmental difference in the degree of the damage showed good correlation with the .beta.-glucuronidase activity in the contents of the lumen in each case, but not with the intestinal tissue ***carboxylesterase*** activity, which converts CPT-11 to its active form (7- ethyl-10-hydroxycamptothecin). Inhibition of the .beta.-glucuronidase activity in the intestinal microflora by antibiotics (1 mg penicillin and 2 mg streptomycin per ml of drinking water) markedly ameliorated the diarrhea and reduced cecal damage. Analysis of CPT-11 and its metabolites in the feces indicated that antibiotics completely inhibited the deconjugation of the glucuronic conjugate of 7-ethyl-10-hydroxycamptothecin by .beta.-glucuronidase. It is suggested that CPT-11-induced diarrhea would be attributable to the damage in the cecum, and that the inhibition of the .beta.-glucuronidase activity in the intestinal microflora is a major protective effect of antibiotics.

L5 ANSWER 66 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 27
AN 96250515 EMBASE
DN 1996250515
TI Identification and properties of a major plasma metabolite of irinotecan (CPT-11) isolated from the plasma of patients.
AU Rivory L.P.; Riou J.-F.; Haaz M.-C.; Sable S.; Vuilhorgne M.; Commercon A.; Pond S.M.; Robert J.
CS Department of Medicine, University of Queensland, Princess Alexandra Hospital, Ipswich.Rd.,Woolloongabba, QLD 4102, Australia
SO Cancer Research, (1996) 56/16 (3689-3694).
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer

029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Irinotecan [7-ethyl-10-14-(1-piperidino)-1- piperidino]carbonyloxycamptoth ecin (CPT-11)] is a promising water-soluble analogue of camptothecin [S. Sawada et al., Chem. and Pharm. Bull. (Tokyo), 39: 1446-1454, 1991]. We have reported previously the presence of an important polar metabolite, in addition to 7-ethyl-10-hydroxycamptothecin (SN-381 .beta.-glucuronide, in samples of plasma taken from patients undergoing treatment with CPT-11 (L. P. Rivory and J. Robert, Cancer Chemother. Pharmacol. 36: 176-179, 1995; L. P. Rivory and J. Robert, J. Cromatogr., 661: 133-141, 1994). Plasma samples (0.5 ml) containing comparatively large amounts of this metabolite were extracted by solid-phase columns and subjected to high-performance liquid chromatography and mass spectrometry in parallel to fluorometric detection. The metabolite yielded [M+1] ions with a m/z of 619, representing the addition of 32 atomic mass units to CPT-11. Purified fractions were subjected to proton nuclear magnetic resonance, and the structure determined, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin (APC), was further validated following synthesis. Like CPT-11, APC was found to be only a weak inhibitor of the cell growth of KB cells in culture (IC50, 2.1 versus 5.5 .mu.g/ml for CPT-11 and 0.01 .mu.g/ml for SN-38, the active metabolite of CPT-11) and was a poor inducer of topoisomerase I DNA-cleavable complexes (100-fold less potent than SN-38). In contrast to CPT-11, APC was not hydrolyzed to SN-38 by human liver microsomes or purified human liver ***carboxylesterase*** . Furthermore, APC did not inhibit the hydrolysis of CPT-11 in these preparations. Interestingly, APC was only a weak inhibitor of acetylcholinesterase in comparison to CPT-11 and neostigmine. It appears likely, therefore, that APC does not contribute directly to the activity and toxicity profile of CPT-11 in vivo.

L5 ANSWER 67 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 96302510 EMBASE
DN 1996302510
TI Pharmacokinetics and pharmacodynamics of irinotecan during a phase II clinical trial in colorectal cancer.
AU Canal P.; Gay C.; Dezeuze A.; Douillard J.Y.; Bugat R.; Brunet R.; Adenis A.; Herait P.; Lokiec F.; Mathieu-Boue A.
CS Centre Claudius Regaud, 20-24 rue du Pont Saint Pierre,31052 Toulouse Cedex, France
SO Journal of Clinical Oncology, (1996) 14/10 (2688-2695).
ISSN: 0732-183X CODEN: JCONDN
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Purpose: A pharmacokinetic study was performed during a phase II clinical trial of irinotecan (CPT-11) to confirm the pharmacokinetic profile of this drug and its metabolite and to investigate interpatient and intrapatient pharmacokinetic variations and pharmacokinetic-pharmacodynamic relationships. Patients and Methods: Twenty-six men and 21 women (mean age, 61 years) with metastatic colorectal cancer, performance status less than 3 (World Health Organization [WHO] scale), and normal renal and hepatic function were administered CPT-11 (350 mg/m2) by 30-minute intravenous (IV) infusion every 21 days. CPT-11 and its metabolites SN-38 and SN-38 glucuronide (SN-38G) were determined by high-performance liquid chromatography (HPLC) using fluorimetric detection. Results: The mean CPT-11 clearance and area under the concentration-time curve (AUC) were 15.2 L/h .cntdot. m2 and 24,769 ng .cntdot. h/mL, respectively. The large difference in SN-38 and SN-38G AUCs (559 v 2,283 ng .cntdot. h/mL) was suggestive of extensive glucuronidation of SN-38. Interindividual variation in the metabolic ratio([AUC(SN-38) + AUC(SN-38G)]/AUC(CPT-11)) was marked (coefficient of variation [CV] = 51.6%] compared with intrapatient variation in this variable (CV = 32.6%). A significant relationship existed between percentage reduction in neutrophil count and the AUC of CPT-11 (r = .597, P < .001) and SN-38 (r = .559, P < .001). No relationship was identified between any pharmacokinetic parameter and delayed diarrhea or therapeutic outcome. Conclusion: Interindividual variations in the metabolic ratio suggest interpatient variation in ***carboxylesterase*** activity. Furthermore, glucuronidation of SN- 38 may also be in part responsible for the large interpatient variability in the total SN-38 AUC. Conversely, low intrapatient variation of this parameter was observed in this study, which indicates a lack of autoinduction of the ***carboxylesterase*** system. The relationship between neutropenia and both CPT- 11 and SN-38 pharmacokinetic parameters confirms the results of previous studies.

L5 ANSWER 68 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 28
AN 96102885 EMBASE
DN 1996102885
TI The role of rat serum ***carboxylesterase*** in the activation of paclitaxel and camptothecin prodrugs.
AU Senter P.D.; Marquardt H.; Thomas B.A.; Hammock B.D.; Frank I.S.; Svensson H.P.
CS B.-M. Squibb Pharmaceut. Res. Inst., 3005 First Avenue,Seattle, WA 98121, United States
SO Cancer Research, (1996) 56/7 (1471-1474).
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Paclitaxel-2-ethylcarbonate (PC) is a prototype for a family of paclitaxel prodrugs that have significant levels of antitumor activities in rodent models for human cancer. In this study, an enzyme responsible for the conversion of PC to paclitaxel was purified from rat serum. N-terminal amino acid sequence analysis indicated that the isolated enzyme was rat serum ***carboxylesterase*** . This enzyme was shown to significantly enhance the cytotoxic activities of both PC and 7-ethyl-10-[4-(1-piperidino)-1- piperidino]carbonyloxycamptothecin (CPT-11), a water-soluble analogue of camptothecin, on lung carcinoma and melanoma cell lines. Rat serum ***carboxylesterase*** may have applications for the site-specific delivery of anticancer drugs to tumor masses.

L5 ANSWER 69 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 29
AN 96310794 EMBASE
DN 1996310794
TI Conversion of irinotecan (CPT-11) to its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38) by human liver ***carboxylesterase*** .
AU Rivory L.P.; Bowles M.R.; Robert J.; Pond S.M.
CS University of Queensland, Department of Medicine, Princess Alexandra Hospital, Ipswich Road,Woolloongabba, QLD 4102, Australia
SO Biochemical Pharmacology, (1996) 52/7 (1103-1111).
ISSN: 0006-2952 CODEN: BCPCA6
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB We have investigated the conversion of the novel anti-topoisomerase I agent CPT-11 (irinotecan; 7-ethyl-10[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin) to its active metabolite, SN-38 (7-ethyl-10-hydroxycamptothecin), by human liver ***carboxylesterase*** (HLC). Production of SN-38 was relatively inefficient and was enzyme deacylation rate-limited with a steady-state phase occurring after 15-20 min of incubation. This later phase followed Michaelis-Menten kinetics with an apparent K(m) of 52.9 .+-. 5.9 .mu.M and a specific activity of 200 .+-. 10 .mu.mol/sec/mol. However, the total enzyme concentration estimated from the intercept concentrations of SN-38 was much lower than that estimated directly from the titration of active sites with paraoxon (0.65 vs. 2.0 .mu.M, respectively). Because deacylation rate-limiting kinetics result in the accumulation of inactive acyl-enzyme complex, we postulated that incubation of CPT-11 with HLC would result in an inhibition of the HLC-catalysed hydrolysis of p-nitrophenylacetate (p-NPA), an excellent substrate for this enzyme. Indeed, this was found to be the case although complete inhibition could not be attained. Analysis of possible kinetic schemes revealed that the most likely explanation for the disparity in estimated enzyme concentrations and the incomplete inhibition of p-NPA hydrolysis is that CPT-11 also interacts at a modulator site on the enzyme, which profoundly reduces substrate hydrolysis. Furthermore, loperamide, a drug often used for the treatment of CFT-11-associated diarrhea, was found to inhibit both CPT-11 and p-NPA HLC-catalysed hydrolysis, most likely by a similar interaction. These observations have direct implications for the clinical use of CPT-11.

L5 ANSWER 70 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1996:563746 BIOSIS
DN PREV199799293102
TI Irinotecan (CPT-11): A brief overview.
AU Rivory, Laurent P.
CS Univ. Queensland, Dep. Med., Princess Alexandra Hosp., Ipswich Road, Woolloongabba, QLD 4102 Australia
SO Clinical and Experimental Pharmacology and Physiology, (1996) Vol. 23, No. 10-11, pp. 1000-1004.
ISSN: 0305-1870.
DT General Review
LA English
AB 1. Irinotecan (also known as CPT-11) is a water soluble, semi-synthetic analogue of 20(S)camptothecin (CPT) with promising activity against a range of tumour types. 2. As with all other active analogues of CPT, irinotecan causes cell toxicity by stabilizing a ternary complex between the nuclear enzyme topoisomerase I (topo I) and double-stranded DNA. This leads to replication fork-arrest, double DNA strand breaks and, possibly, illegitimate recombination of vital genes. 3. This activity is much greater for its metabolite SN-38 and irinotecan is widely considered to be a prodrug of SN-38. 4. The anti-topo I activity of CPT is stereoselective at C-20 and irinotecan is synthesized from 20(S)CPT to ensure maximal activity. In aqueous solutions, the lactone ring of CPT undergoes reversible and spontaneous hydrolysis to a ring-opened and inactive carboxylate form. In patients, it has been shown that the lactone is the predominant form of SN-38 in plasma, whereas the opposite is true for irinotecan. 5. The transformation of irinotecan to SN-38 is catalysed by

carboxylesterases. However, this conversion appears relatively inefficient in man. 6. Irinotecan and SN-38 show evidence of other metabolic reactions (type I and 11), some of which could be subject to pharmacogenetic variability. 7. Therapy with irinotecan is associated with unusual toxicities, such as an acute cholinergic-like syndrome and delayed onset diarrhoea. Although the mechanism for the diarrhoea remains to be defined, the cholinergic toxicity appears to be due to an inhibition of acetylcholinesterase.

L5 ANSWER 71 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 96298767 EMBASE
DN 1996298767
TI Combination of irinotecan hydrochloride (CPT-11) and Cisplatin as a new regimen for patients with advanced ovarian cancer.
AU Sugiyama T.; Nishida T.; Kataoka A.; Imaishi K.; Komai K.; Ushijima K.; Hasuo Y.
CS Department of Obstetrics/Gynecology, Kurume University School of Medicine,Kurume, Japan
SO Acta Obstetrica et Gynaecologica Japonica, (1996) 48/9 (827-834). ISSN: 0300-9165 CODEN: AOGLAR
CY Japan
DT Journal; Article
FS 010 Obstetrics and Gynecology
016 Cancer
037 Drug Literature Index
038 Adverse Reactions Titles
LA Japanese
SL English; Japanese
AB It has been reported that the antitumor effect of CPT-11 is manifested through the inhibition of topoisomerase 1 by SN-38 which active netabolite of CPT 11 produced by intracellular ***carboxylesterase*** , and that CPT-11 is effective against recurrent ovarian carcinoma. We investigated the antitumor effect and adverse reactions in the combined therapy with CPT-11 and CDDP in 15 patients with prior chemotherapy for current carcinoma therapy with CPT 11 and CDDP in 15 patients with prior chemotherapy for recurrent carcinoma and in 7 patients without prior chemotherapy, consisting of 4 patients with postoperative adjuvant chemotherapy for clear cell carcinoma and 3 patients with metastic ovarian carcinoma. CDDP was administered on day 1 and CPT-11 was administered three times on days 1, 8 and 15. The dose of both CDDP and CPT-11 was 50mg/m2 or 60mg/m2. Adverse reactions were investigated in all patients and the antitumor effect was assessed in 12 patients with recurrent carcinoma who had measurable lesions. (1) The DLF was neutropenia. The neutrophil count nadiar occurred on day 18 or 19. Grade 3 or 4 adverse reactions were observed in 60% or more of the patients, but they disappeared following short term administration of G-CSF. In patients with recurrent carcinoma given CDDP and CPT-11 at 60mg/m2 the incidence of grade 3 or 4 adverse reaction and number of occasions on which CPT-11 administration had to be postponed were higher than those in patients given 50gm/m2. (2) Mild platelet reduction was observed. (3) Grade 3 or 4 diarrhea was observed in 3.2% of patients with recurrent carcinoma and in 7.7% of patients with metastic ovarian carcinoma. (4) The antitumor effect was evaluated in 12 patients with recurrent carcinoma : CR in 2 patients PR in 3, NC in 6, and PD in one. The response rate was 41.7%. (5) An antitumor effect was observed in 2 patients with serons carcinoma an in one patient each with mucons carcinoma, clear cell carcinomas and endometrioid carcinoma. In conclusion, adverse reaction caused by the combination therapy with CPT-11 and CDDP (CPT- 11 : 50 - 60mg/m2 on days 1, 8 and. 15 CDDP : 50 - 60mg/m2 on day 1) can be relieved by short term administration of G-CSF and it is suggested that the combination therapy may be effective in treating ovarian carcinoma.

L5 ANSWER 72 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 96313067 EMBASE
DN 1996313067
TI Irinotecan: A review of its pharmacological properties and clinical efficacy in the management of advanced colorectal cancer.
AU Wiseman L.R.; Markham A.
CS Adis International Limited, Private Bag 65901, 41 Centorian Drive,Mairangi Bay, Auckland 10, New Zealand
SO Drugs, (1996) 52/4 (606-623). ISSN: 0012-6667 CODEN: DRUGAY
CY New Zealand
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LA English
SL English
AB Irinotecan (CPT-II) is a semisynthetic derivative of camptothecin. It and other camptothecin analogues/derivatives appear to exert their antitumour activity by binding to topoisomerase I. The active metabolite of irinotecan, 7-ethyl-10-hydroxycamptothecin (SN-38), has demonstrated potent growth inhibition of human colorectal cancer cells in vitro, with superior activity to fluorouracil. In phase II clinical studies in patients with advanced colorectal cancer objective response rates after irinotecan therapy ranged between 20.5 and 32%. These studies used a range of irinotecan regimens including 350 mg/m2 once every 3 weeks (Europe), 125 to 150 mg/m2 once a week for 4 weeks followed by a 2-week drug-free interval (US) and 100 mg/m2/week or 150 mg/m2 every 2 weeks (Japan). The median duration of response ranged between 5.6 and 10.6 months. Disease stabilisation occurred in 30 to 71.2% of patients. Objective response rates to irinotecan therapy in patients who had received no prior chemotherapy were similar to those in patients treated with fluorouracil. Importantly irinotecan also induced responses in some patients with tumours refractory to fluorouracil. Severe (grade 3 or 4) neutropenia and diarrhoea, which occurred in up to 40% of patients receiving irinotecan therapy in phase II studies, require careful monitoring and appropriate management Thus, irinotecan is a valuable agent for the second-line treatment of patients with advanced colorectal cancer who fail to respond to or relapse after fluorouracil therapy.

L5 ANSWER 73 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1996:255318 BIOSIS
DN PREV199698811447
TI The identification and properties of a major metabolite of irinotecan (CPT-11) isolated from the plasma of patients.
AU Rivory, L. P. (1); Riou, J. F.; Pond, S. M. (1); Haaz, M. C.; Sable, S.; Vuilhorgne, M.; Commercon, A.; Robert, J.
CS (1) Univ. Queensland, Brisbane, QLD Australia
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1996) Vol. 37, No. 0, pp. 177.
Meeting Info.: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996
ISSN: 0197-016X.
DT Conference
LA English

L5 ANSWER 74 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 30
AN 96334955 EMBASE
DN 1996334955
TI Future directions for clinical research with CPT-11 (irinotecan).
AU Von Hoff D.
CS Institute for Drug Development, Texas Research Park, 14960 Omicron Park,San Antonio, TX 78245, United States
SO European Journal of Cancer Part A, (1996) 32/SUPPL. 3 (S9-S12). ISSN: 0959-8049 CODEN: EJCTEA
PUI S 0959-8049(96)00291-2
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB CPT-11 is a new agent with a unique mechanism of action, namely the inhibition of topoisomerase I. An examination of data from the laboratory reveals several leads which should be pursued in the clinic. A dose-response effect for CPT-11 activity has been noted in the human tumour cloning assay. CPT-11 has activity against breast and mesothelioma colony-forming units in a human tumour cloning assay, and has in vivo activity against a number of paediatric malignancies. Promising combinations in preclinical in vivo models include CPT-11/mitomycin C and CPT-11/cytosine arabinoside. There is incomplete cross-resistance among topoisomerase I inhibitors, suggesting that combinations of topoisomerase I inhibitors should be investigated. Several natural products have been identified which have potential to decrease CPT-11-induced diarrhoea. The level of ***carboxylesterase*** in a patient's tumour appears to be related to the in vitro activity of CPT-11, suggesting that measurement of ***carboxylesterase*** in a patient's tumour could be used to identify patients who are most likely to respond to treatment with CPT-11. These preclinical findings suggest substantial further clinical potential for CPT-11 in terms of decreased CPT-11-induced diarrhoea as well as increased antitumour activity, which should be explored in phase I and II studies.

L5 ANSWER 75 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 31
AN 95257013 EMBASE
DN 1995257013
TI A new water-soluble camptothecin derivative, DX-8951f, exhibits potent antitumor activity against human tumors in vitro and in vivo.
AU Mitsui I.; Kumazawa E.; Hirota Y.; Aonuma M.; Sugimori M.; Ohsuki S.; Uoto K.; Ejima A.; Terasawa H.; Sato K.
CS Exploratory Research Laboratories I, Dalichi Pharmaceutical Co. Ltd., 16-13 Kitakasai 1-chome,Edogawa-ku, Tokyo 134, Japan
SO Japanese Journal of Cancer Research, (1995) 86/8 (776-782). ISSN: 0910-5050 CODEN: JJCREP
CY Japan
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB CPT-11, a semisynthetic derivative of camptothecin, exhibited strong antitumor activity against lymphoma, lung cancer, colorectal cancer, gastric cancer, ovarian cancer, and cervical cancer. CPT-11 is a pro-drug that is converted to an active metabolite, SN-38, in vivo by enzymes such as ***carboxylesterase*** . We synthesized a water soluble and non-pro drug analog of camptothecin, DX-8951f. It showed both high in vitro potency against a series of 32 malignant cell lines and significant topoisomerase I inhibition. The anti-proliferative activity of DX-8951f,

as indicated by the mean GI50 value, was about 6 and 28 times greater than that of SN-38 or SK and F 10486-A (Topotecan), respectively. These three derivatives of camptothecin showed similar patterns of differential response among 32 cell lines, that is, their spectra of in vitro cytotoxicity were almost the same. The antitumor activity of three doses of DX-8951f administered i.v. at 4 day intervals against human gastric adenocarcinoma SC-6 xenografts was greater than that of CPT-11 or SK and F 10486-A. Moreover, it overcame P-glycoprotein-mediated multi-drug resistance. These data suggest that DX-8951f has a high antitumor activity and is a potential therapeutic agent.

L5 ANSWER 76 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 95192101 EMBASE
DN 1995192101
TI Partial purification and characterization of an esterase acting on the anticancer pro-drugs, 7-ethylcamptothecin derivatives.
AU Fujita Y.; Yaegashi T.; Sawada S.; Oyama H.; Yoshimoto T.; Tsuru D.
CS Department of Applied Microbiology, Kamamoto Institute of Technology, Ikeda 4-22-1,Kumamoto 860, Japan
SO Biological and Pharmaceutical Bulletin, (1995) 18/5 (648-652).
ISSN: 0918-6158 CODEN: BPBLEO
CY Japan
DT Journal; Article
FS 016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
AB A hydrolytic enzyme which catalyzes hydrolysis of the ester-linkage of a series of 17-O-acyl derivatives of 7-ethylcamptothecin-21-(2-dimethylamino)ethylamide[acyl derivatives of 22E] was purified from rat liver and its properties were characterized. It hydrolyzed the ester-linkage of all 22E derivatives tested as well as p-nitrophenyl acetate at pH 8-9 but had no effect on 7-ethyl-10-[4-(piperidino)-1-piperidino] carbonyloxycamptothecin (CPT-11: irinotecan), unlike CPT-11 converting ***carboxylesterase*** , which was previously purified from rat serum [Tsuji T. et al., J. Pharmacobio-Dyn., 14, 341 (1991)]. The enzyme had no effect on either acetyl choline or butyrylcholine. It was inhibited by several organophosphorous compounds such as diisopropyl fluorophosphate (DFP), bis-(p-nitrophenyl)phosphate and paraoxon, but was insensitive to inhibitors specific for choline esterases. These results indicate that this liver esterase is clearly distinct from choline esterase and serum CPT-11 converting enzyme and is able to convert pro-drugs, O-acyl derivatives of 22E, to an antitumor agent.

L5 ANSWER 77 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 32
AN 95055072 EMBASE
DN 1995055072
TI Intracellular carboxyl esterase activity is a determinant of cellular sensitivity to the antineoplastic agent KW-2189 in cell lines resistant to cisplatin and CPT-P1.
AU Ogasawara H.; Nishio K.; Kanzawa F.; Lee Y.-S.; Funayama Y.; Ohira T.; Kuraishi Y.; Isogai Y.; Saijo N.
CS Pharmacology Division, Nat. Cancer Center Research Inst., Tsukiji 5-1-1,Chuo-ku, Tokyo 104, Japan
SO Japanese Journal of Cancer Research, (1995) 86/1 (124-129).
ISSN: 0910-5050 CODEN: JJCREP
CY Japan
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB KW-2189, a novel antitumor antibiotic belonging to the duocarmycins, possesses marked DNA-binding activity upon activation by carboxyl esterase to its active form, DU-86. Three duocarmycins, KW-2189, DU-86 and duocarmycin SA, were active against the cisplatin (CDDP) resistant human non-small cell lung cancer cell lines PC-9/CDDP and PC-14/CDDP, and the multidrug-resistant human small cell lung cancer cell line H69/VP. However, HAC2/0.1, a CDDP-resistant human ovarian cancer cell line which is also resistant to CPT-11 because of decreased intracellular activation of CPT-11, was about 12.8-fold more resistant to KW-2189. HAC2/0.1 was not resistant to other duocarmycins as compared to its parental cell line, HAC2. There was no difference between HAC2 and HAC2/0.1 with regard to the intracellular accumulation of KW-2189. Addition of 130 mU/ml of carboxyl esterase to the culture medium did not influence the sensitivity of HAC2 cells to KW-2189. However, the sensitivity of HAC2/0.1 cells to KW-2189 was enhanced to the level of HAC2. These results suggest that HAC2/0.1 is less potent than HAC2 in activating KW-2189. The carboxyl esterase activity of whole-cell and microsomal extracts from HAC2/0.1 was approximately 60% of that from HAC2. The cell-free experiment revealed that KW-2189 bound to DNA more efficiently in the presence of HAC2 than HAC2/0.1 cell extract. It was concluded that decreased intracellular carboxyl esterase activity in HAC2/0.1 cells caused decreased intracellular conversion of KW-2189.to its active form, thus producing resistance to KW-2189. The decreased conversion of CPT-11 to SN-38 38 in HAC2/0.1 cells might be explained by decreased carboxyl esterase activity.

L5 ANSWER 78 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 94233185 EMBASE
DN 1994233185
TI Simultaneous administration of CPT-11 and fluorouracil: Alteration of the pharmacokinetics of CPT-11 and SN-38 in patients with advanced colorectal cancer [2].
AU Sasaki Y.; Ohtsu A.; Shimada Y.; Ono K.; Saijo N.
CS Division of Oncology/Hematology, Department of Medicine, National Cancer Center Hospital East, 6-5-1 Kashiwanoha,Kashiwa City, Chiba 277, Japan
SO Journal of the National Cancer Institute, (1994) 86/14 (1096-1098).
ISSN: 0027-8874 CODEN: JNCIAM
CY United States
DT Journal; Letter
FS 016 Cancer
037 Drug Literature Index
LA English

L5 ANSWER 79 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 33
AN 94181425 EMBASE
DN 1994181425
TI Metabolic activation of CPT-11, 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin, a novel antitumor agent, by ***carboxylesterase*** .
AU Satoh T.; Hosokawa M.; Atsumi R.; Suzuki W.; Hakusui H.; Nagai E.
CS Biochem. Pharmacol./Biotoxicol. Lab., Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho,Inage-ku, Chiba 263, Japan
SO Biological and Pharmaceutical Bulletin, (1994) 17/5 (662-664).
ISSN: 0918-6158 CODEN: BPBLEO
CY Japan
DT Journal; Article
FS 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB We measured the plasma concentrations of 7-ethyl-10-[4-(1-piperidino)-1-piperidine]carbonyloxycamptothecin (CPT-11) and the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38), after treatment with CPT-11 to rats pretreated with bis-p-nitrophenylphosphate (BNPP) which is a specific inhibitor of ***carboxylesterase*** , and non-pretreated rats. The plasma level of SN-38 was decreased in the BNPP-pretreated group compared with these of non- pretreated group, indicating that the esterase involved in CPT-11 metabolism is a ***carboxylesterase*** . We also characterized the molecular species of ***carboxylesterase*** involved in CPT-11 metabolism using enzyme preparations purified from liver microsomes. Thirteen ***carboxylesterase*** isozyme activities towards CPT-11 were compared and guinea pig GLP1 was found to have the highest activity, while human HU1 isozyme had relatively lower activity than those of animal species. In studies on the kinetic parameters of the hydrolysis of CPT-11 by the purified ***carboxylesterase*** isozymes the highest V(max) value of the isozymes was found in human HU1 and the smallest was seen in rat RL1. The V(max)/K(m) for RL1 showed the largest value of 21.7 nmol/mg protein/mM.

L5 ANSWER 80 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1994:289955 BIOSIS
DN PREV199497302955
TI Human tumor ***carboxylesterase*** activity correlates with CPT-11 cytotoxicity in vitro.
AU Chen, S.-F.; Rothenberg, M. L.; Clark, G.; Degen, D.; Wajima, M.; Barton, D.; Von Hoff, D. D.
CS Inst. Drug Dev., CTRC, San Antonio, TX 78245 USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1994) Vol. 35, No. 0, pp. 365.
Meeting Info.: 85th Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 10-13, 1994
ISSN: 0197-016X.
DT Conference
LA English

L5 ANSWER 81 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 94124366 EMBASE
DN 1994124366
TI Topoisomerase I inhibitors: An overview of the camptothecin analogs.
AU Burris III H.A.; Fields S.M.
CS Cancer Therapy and Research Center, 8122 Datapoint Drive,San Antonio, TX 78229, United States
SO Hematology/Oncology Clinics of North America, (1994) 8/2 (333-355).
ISSN: 0889-8588 CODEN: HCNAEQ
CY United States
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The topoisomerase I inhibitors are an exciting new class of antineoplastic agents currently under clinical development. Analogues of camptothecin with improved toxicity profiles and antitumor activity included CPT-11 and topotecan. CPT-11 has demonstrated activity against a variety of tumor types, particularly colon and lung cancer. Early results with topotecan against ovarian and lung cancer are also encouraging. Combination trials with other antineoplastic agents including cisplatin and etoposide, and

early clinical trials with new topoisomerase I inhibitors, such as 9-aminocamptothecin, are underway.

L5 ANSWER 82 OF 83 BIOSIS COPYRIGHT 2002 BIOSIS
AN 1992:403698 BIOSIS
DN BR43:59573
TI ROLE OF ***CARBOXYLESTERASE*** ON METABOLISM OF CAMPTOTHECIN ANALOG
CPT-11 IN NON-SMALL CELL LUNG CANCER CELL LINE PC-7 CELLS.
AU KANZAWA F; KONDOH H; KWON S J; SAIJO N
CS PHARMACOLOGY DIVISION, NATIONAL CANCER CENTER RESEARCH INSTITUTE, CHUO-KU,
TOKYO 104, JPN.
SO 83RD ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, SAN
DIEGO, CALIFORNIA, USA, MAY 20-23, 1992. PROC AM ASSOC CANCER RES ANNU
MEET. (1992) 33 (0), 427.
CODEN: PAMREA.
DT Conference
FS BR; OLD
LA English

L5 ANSWER 83 OF 83 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 34
AN 91233660 EMBASE
DN 1991233660
TI CPT-11 converting enzyme from rat serum: Purification and some properties.
AU Tsuji T.; Kaneda N.; Kado K.; Yokokura T.; Yoshimoto T.; Tsuru D.
CS School of Pharmaceutical Sciences, Nagasaki University, Bunkyo-machi 1-14, Nagasaki 852, Japan
SO Journal of Pharmacobio-Dynamics, (1991) 14/6 (341-349).
ISSN: 0386-846X CODEN: JOPHDQ
CY Japan
DT Journal; Article
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB A rat serum enzyme that catalyzes the conversion of a pro-drug, 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin (CPT-11), to an anticancer drug, 7-ethyl-10-hydroxy-camptothecin (SN-38), was purified and its properties were characterized. The enzyme was purified by column chromatography on diethylaminoethyl Toyopearl 650M, QAE-Sephadex, Sephadex G-150, Con A-Sepharose and high performance liquid
chromatography with an ion-exchanger column. It was most active at pH 7.5 and was stable at pH 4-9 for 1 h at 30.degree.C. The molecular weight was estimated to be 60 and 57 kDa by gel filtration and sodium dodecylsulfate-polyacrylamide gel electrophoresis methods, respectively, and the isoelectric point was 4.6, as determined by isoelectric focusing. The K(m) value for CPT-11 was 0.28 .mu.M. This enzyme was inhibited by diisopropyl phosphorofluoridate (DFP) and phenylmethanesulfonyl fluoride (PMSF) but insensitive to eserine, p-chloromercuribenzoate (PCMB) and ethylenediaminetetraacetate (EDTA). The enzyme also hydrolyzed p-nitrophenylacetate (p-NPA), a commonly used substrate for esterases, but was not active toward acetylcholine, suggesting that the enzyme is a ***carboxylesterase*** [EC 3.1.1.1]. During the hydrolyses of CPT-11 and p-NPA, an initial burst phenomenon similar to that found in the .alpha.-chymotrypsin-catalyzed hydrolysis of p-NPA was observed. Kinetic analysis revealed that the deacylation of the enzyme is the rate-limiting step in substrate hydrolysis. This enzyme was found to also split other ester derivatives of SN-38 besides CPT-11.

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L1 4 S IRINOTECAN
L2 1 S CPT-11

FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 13:24:14 ON 17 JAN 2002
L3 3200 S L2
L4 133 S L3 AND (CARBOXYLESTERASE OR CE)
L5 83 DUP REM L4 (50 DUPLICATES REMOVED)

FILE 'HOME' ENTERED AT 13:31:32 ON 17 JAN 2002

FILE 'STNGUIDE' ENTERED AT 13:31:36 ON 17 JAN 2002

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FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 13:49:27 ON 17 JAN 2002

FILE 'EMBASE, BIOSIS, CAPLUS' ENTERED AT 13:49:57 ON 17 JAN 2002

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 13:50:52 ON 17 JAN 2002

FILE 'STNGUIDE' ENTERED AT 14:04:11 ON 17 JAN 2002

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=> s metaboliz? enzyme and (prodrug or pro-drug) and conver? and (polynucleotide or DNA or gene)
L6 4 METABOLIZ? ENZYME AND (PRODRUG OR PRO-DRUG) AND CONVER? AND
(POLYNUCLEOTIDE OR DNA OR GENE)

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7 3 DUP REM L6 (1 DUPLICATE REMOVED)

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L7 ANSWER 1 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000076876 EMBASE
TI Secreted human .beta.-glucuronidase: A novel tool for ***gene*** -directed enzyme ***prodrug*** therapy.
AU Weyel D.; Sedlacek H.-H.; Muller R.; Brusselbach S.
CS R. Muller, IMT, Philipps-University Marburg, Emil-Mannkopff-Strasse 2, D-35033 Marburg, Germany
SO Gene Therapy, (2000) 7/3 (224-231).
Refs: 29
ISSN: 0969-7128 CODEN: GETHEC
CY United Kingdom
DT Journal; Article
FS 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB A major problem of tumor ***gene*** therapy is the low transduction efficiency of the currently available vectors. One way to circumvent this problem is the delivery of therapeutic genes encoding intracellular enzymes for the ***conversion*** of a ***prodrug*** to a cytotoxic drug which can then spread to neighboring non-transduced cells (bystander effect). One possibility to improve the bystander effect could be the extracellular ***conversion*** of a hydrophilic ***prodrug*** to a lipophilic, cell-permeable cytotoxic drug. Toward this end, we have used a secreted form of the normally lysosomal human .beta.-glucuronidase (s-.beta.Gluc) to establish an extracellular cytotoxic effector system that ***converts*** an inactivated glucuronidated derivative of doxorubicin (HMR 1826) to the cytotoxic drug. We demonstrate that s-.beta.Gluc-transduced tumor cells ***convert*** HMR 1826 to doxorubicin which is taken up by both transduced and non-transduced cells. s-.beta.Gluc in combination with HMR 1826 efficiently induces tumor cell killing both in cell culture and in vivo. This effect is mediated through a pronounced bystander effect of the generated cytotoxic drug. Most notably, this ***gene*** therapeutic strategy is shown to be clearly superior to conventional chemotherapy with doxorubicin.

=> d bib abs 2-
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L7 ANSWER 2 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 97319346 EMBASE
DN 1997319346
TI Detection of cytosine deaminase in genetically modified tumor cells by specific antibodies.
AU Haack K.; Moebius U.; Knebel Doeberitz M.V.; Herfarth Ch.; Schackert H.-K.; Gebert J.F.
CS Dr. J.F. Gebert, Sekt. Molekulare Diagnostik Therapie, Chirurgische Universitatsklinik, Im Neuenheimer Feld 116, D-69120 Heidelberg, Germany
SO Human Gene Therapy, (1997) 8/11 (1395-1401).
Refs: 30
ISSN: 1043-0342 CODEN: HGTHE3
CY United States
DT Journal; Article
FS 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Bacterial cytosine deaminase (CD) ***converts*** the non-toxic ***prodrug*** 5-fluorocytosine (5-FC) into 5-fluorouracil (5-FU), which is toxic for mammalian cells. Therefore, the CD ***gene*** is used in cancer ***gene*** therapy to achieve high local concentration of a toxic metabolite without significant systemic toxicity. To allow the detection of CD expression at the protein level, we raised both polyclonal rabbit antisera and a monoclonal antibody (mAb) against a histidine-tagged CD fusion protein. The specificity of the polyclonal antisera and the mAb was confirmed by immunohistochemistry, immunoblot analysis, and immunoprecipitation using CD-expressing tumor cell lines. Furthermore, the antibodies can be used for ELISA assays and flow cytometry. Finally, the CD protein could be demonstrated in frozen tissue sections of CD-modified tumors in a rat tumor model using the anti-CD serum. With these antibodies, CD expression can now be monitored throughout in vitro and in viva ***gene*** transfer studies, including clinical protocols relying on the CD suicide ***gene*** strategy.

L7 ANSWER 3 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
AN 1998085073 EMBASE
TI Genetic ***prodrug*** activation therapy.
AU Rigg A.; Sikora K.
CS A. Rigg, ICRF Molecular Oncology Unit, Imperial College of Medicine, Hammersmith Hospital, Du Cane Road, London W12 0NN, United Kingdom. a.rigg@icrf.icnet.uk
SO Molecular Medicine Today, (1997) 3/8 (359-366).
Refs: 47
ISSN: 1357-4310 CODEN: MMTOFK
CY United Kingdom
DT Journal; General Review
FS 022 Human Genetics
026 Immunology, Serology and Transplantation
LA English
SL English
AB Genetic ***prodrug*** activation therapy shows promise as a therapeutic option for the treatment of cancer as well as a variety of other diseases. It involves the insertion of a ***gene*** encoding a drug- ***metabolizing*** ***enzyme*** into cells and the systemic administration of a ***prodrug*** . The ***prodrug*** is ***converted*** to a cytotoxic agent by the action of the expressed enzyme. To ensure that the enzyme is only expressed in the targeted subset of cells, the transcriptional apparatus of a ***gene*** that is unique to this subset is used to regulate the ***gene*** encoding the drug-***metabolizing*** ***enzyme*** . As with all types of ***gene*** therapy, one of the major obstacles to successful clinical treatment is the development of safe and effective ***gene*** delivery systems.

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FILE 'CAPLUS' ENTERED AT 14:34:24 ON 17 JAN 2002
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=> s l1
L2 3200 L1

=> s l2 and (carboxylesterase or CE)
L3 133 L2 AND (CARBOXYLESTERASE OR CE)

=> s l3 and APC
L4 8 L3 AND APC

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 6 DUP REM L4 (2 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 6 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 6 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001379246 EMBASE
TI A new metabolite of irinotecan in which formation is mediated by human hepatic cytochrome P-450 3A4.
AU Sai K.; Kaniwa N.; Ozawa S.; Sawada J.
CS K. Sai, Division of Xenobiotic Metablism, Nat'l Inst. of Hlth. Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan. sai@nihs.go.jp
SO Drug Metabolism and Disposition, (2001) 29/11 (1505-1513).
Refs: 31
ISSN: 0090-9556 CODEN: DMDSAI
CY United States
DT Journal; Article
FS 022 Human Genetics
030 Pharmacology.
037 Drug Literature Index
LA English
SL English
AB Irinotecan (CPT-11) is an anticancer prodrug. It is converted by ***carboxylesterase*** to yield an active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), which acts as a topoisomerase I inhibitor. Several oxidative metabolites of CPT-11 have been identified in humans, including 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin (***APC***) and 7-ethyl-10-(4-amino-1-piperidino)carbonyloxycamptothecin (NPC), generated by cytochrome P-450 3A4 (CYP3A4). Other minor metabolites in which metabolic pathways and biologic activities have not been identified also exist. To further investigate the metabolism of CPT-11 in human liver, we analyzed metabolites of CPT-11 in human hepatic microsomes using a high-performance liquid chromatography/mass spectrometry (HPLC/MS) system and detected a new metabolite that was the major one produced in the microsomal system. HPLC-tandem mass spectrometry (HPLC/MS/MS) analysis indicated that this compound was an oxidation product formed by the loss of two hydrogen atoms from the terminal piperidine ring. Kinetic analyses indicated that a single enzyme generated the metabolite, and we have identified this enzyme in two in vitro systems. The formation of the new metabolite was significantly inhibited by SKF525A, ketoconazole, and an anti-CYP3A4 antibody and catalyzed specifically by CYP3A4 expressed in insect microsomes. A significant correlation was observed between the generation of this metabolite and the CYP3A4 content in individual human hepatic microsomes. These findings indicate that this newly detected metabolite is a CYP3A4-generated product that may be produced in hepatic microsomes of patients treated with CPT-11.

L5 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 1999:549389 CAPLUS
DN 131:165300
TI Rabbit liver ***carboxylesterase*** capable of activating chemotherapeutic prodrug and thereby sensitizing and inhibiting growth of human tumor cells
IN Danks, Mary K.; Potter, Philip M.; Houghton, Peter J.
PA St. Jude Children's Research Hospital, USA
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9942593	A1	19990826	WO 1999-US3171	19990212
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9928679	A1	19990906	AU 1999-28679	19990212
EP 1054979	A1	20001129	EP 1999-909488	19990212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI US 1998-75258	A2	19980219		
WO 1999-US3171	W	19990212		

AB Polynucleotides encoding a ***carboxylesterase*** enzyme and polypeptides encoded by the polynucleotides which are capable of metabolizing the chemotherapeutic prodrug CPT-11 (Irinotecan) and its inactive metabolite ***APC*** to active SN-38 drug (7-ethyl-10-hydroxycamptothecin) are provided. Complementary DNA encoding a ***carboxylesterase*** was cloned from rabbit liver and shown to differ from the published sequence (G. Kurza and J. Ozois, 1988) of rabbit liver ***carboxylesterase*** . This enzyme was 60-fold more active with CPT-11 than the endogenous human enzyme, and use of this enzyme in combination with ***APC*** renders the inactive metabolite a useful chemotherapeutic prodrug. Compns. comprising a polynucleotide of the present invention and a disease-specific responsive promoter (e.g., the ornithine decarboxylase promoter responsive to c-myc) can be delivered to selected tumor cells to sensitize the tumor cells to the chemotherapeutic prodrug CPT-11, thereby inhibiting tumor cell growth. Another method for delivering the ***carboxylesterase*** to selected tumor cells involves antibody direct enzyme prodrug therapy (ADEPT). Rabbit ***carboxylesterase*** /prodrug compns. can also be used to purge bone marrow of tumor cells, thereby preventing minimal residual disease. In addn., screening assays for identification of drugs activated by this enzyme are described.
RE.CNT 9
RE
(1) Alexson, S; J Biol Chem 1994, V269(25), P17118 CAPLUS
(2) Danks, M; Cancer Research 1998, V58, P20 CAPLUS
(3) Miller, S; J Biol Chem 1980, V255(15), P7161 CAPLUS
(4) Mullen; WO 93/01281 A1 1993 CAPLUS
(5) Potter, P; Cancer Research 1998, V58, P2646 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 6 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
AN 1999000767 EMBASE
TI Conversion of the CPT-11 metabolite ***APC*** to SN-38 by rabbit liver ***carboxylesterase*** .
AU Guichard S.M.; Morton C.L.; Krull E.J.; Stewart C.F.; Danks M.K.; Potter P.M.
CS M.K. Danks, Department of Molecular Pharmacology, St. Jude Children's Res. Hospital, 332 North Lauderdale, Memphis, TN 38105, United States.

mary.danks@stjude.org
SO Clinical Cancer Research, (1998) 4/12 (3089-3094).
Refs: 17
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
AB The anticancer drug CPT-11 (7-ethyl-[4(1-piperidino)1-piperidino]carbonyloxycamptothecin) is a water-soluble derivative of camptothecin. We report here the conversion of ***APC*** (7-ethyl-[4-N-(5- aminopentanoic acid)-l-piperidino] carbonyloxycamptothecin), an inactive metabolite of CPT-11, to SN-38 (7-ethyl-10-hydroxycamptothecin), the active metabolite of CPT-11, by a rabbit liver ***carboxylesterase*** . This reaction is not catalyzed by any known human enzyme. The formation of SN-38 from ***APC*** was characterized by an apparent K(m) of 37.9 .+-. 7.1 .mu.M and a V(max) of 16.9 .+-. 0.9 pmo/units/min. SN-38 was confirmed as a reaction product by high- performance liquid chromatography and mass spectrometry. A 24-h incubation of 10 .mu.M ***APC*** with 500 units/ml of rabbit ***carboxylesterase*** produced 4 .mu.M SN- 38. The product of this reaction inhibited the growth of U373 MG human glioblastoma cells in vitro. The IC50 for a 24-h exposure of U373 MG cells to ***APC*** in the presence of 50 units/ml of rabbit ***carboxylesterase*** was 0.27 .+-. 0.08 .mu.M, whereas ***APC*** alone demonstrated no inhibition of growth at concentrations up to 1 .mu.M. The IC50 of U373 MG cells transfected with the cDNA encoding the rabbit ***carboxylesterase*** (U373pIRESrabbit) and exposed to ***APC*** for 24 h was 0.8 .+-. 0.1 .mu.M ***APC*** , whereas the growth of cells transfected with vector control (U373pIRES) was unaffected by up to 1 .mu.M ***APC*** . Because ***APC*** is nontoxic to human cells, we are investigating the possibility of using ***APC*** /rabbit ***carboxylesterase*** in a prodrug/enzyme therapeutic approach.

L5 ANSWER 4 OF 6 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998376263 EMBASE
TI Pharmacology of irinotecan.
AU Robert J.; Rivory L.
CS J. Robert, Institut Bergonie, Universite Victor Segalen Bordeaux 2, 180 rue de Saint-Genes, 33076 Bordeaux Cedex, France
SO Drugs of Today, (1998) 34/9 (777-803).
Refs: 187
ISSN: 0025-7656 CODEN: MDACAP
CY Spain
DT Journal; General Review
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Irinotecan (CPT-11) is a semisynthetic derivative of camptothecin, an alkaloid extracted from the Chinese plant Camptotheca acuminata. It bears a bis-piperidine moiety and was selected for its water solubility and promising preclinical antitumor activity in in vitro and in vivo models. The target of drugs of the camptothecin family is DNA topoisomerase I, a nuclear enzyme involved in the relaxation of the DNA double helix required for replication and transcription activities. They stabilize the enzyme-DNA complex and prevent the religation of the single-strand breaks created by the enzyme, which are converted to double-strand breaks upon the collision with a replication fork during the S-phase. Resistance to irinotecan appears not to be mediated by P-glycoprotein, but by qualitative and/or quantitative alterations of its target, topoisomerase I, or by alterations occurring downstream of this interaction. As with all camptothecin derivatives, irinotecan contains a lactone ring that can be spontaneously and reversibly hydrolyzed to a carboxylate open ring form, which predominates at neutral and alkaline pH and is inactive on topoisomerase I-DNA complexes. Irinotecan is, in fact, much less active than its metabolite SN-38 and is generally considered as a prodrug of this compound. The ***carboxylesterase*** which carries out this conversion is preferentially active on the lactone form of irinotecan and directly generates the lactone form of SN-38, which may explain the superiority of irinotecan overs SN-38 in vivo. Further metabolism of SN-38 to a beta-glucuronide conjugate is a major pathway of detoxification and plays an important role in determining the irinotecan toxicity in the clinical setting. Other metabolic pathways of irinotecan involve oxidations occurring on the bis-piperidine rings, which are carried out by cytochrome P450. Irinotecan has shown an important activity in advanced and metastatic colorectal carcinoma and is now used for this indication in several countries, with two different recommended schedules: weekly administration of 125 mg/m2 with a 2-week drug-free interval every 4 administrations or 3- weekly administration of 350 mg/m2, a dose that can be increased to 500 mg/m2 with the support of antidiarrhetics. Other possible indications of irinotecan include lung and cervix cancer, which are presently under investigation. The dose-limiting toxicity of irinotecan is mainly diarrhea, which occurs 7-10 days after treatment and can be life-threatening when associated with neutropenia, another frequent side effect. High-dose loperamide has shown good efficacy for treating this diarrhea and has allowed an increase in irinotecan doses tolerated by patients. The pharmacokinetics of irinotecan are characterized by a 2- or 3-compartment decay, with a terminal half-life of about 10 h, a total volume of distribution of 150 l/m2 and a total plasma clearance of 15 l/h/m2. SN-38 AUC is only a small fraction of that of irinotecan (2-4%) and SN-38 is eliminated from plasma with a half-life of about 2 h. SN-38 glucuronide is present in plasma at higher concentrations that SN-38 and is eliminated at the same time rate. ***APC*** , produced by the action of cytochrome P450, isoenzyme 3A4, is present in plasma at concentrations close to those of irinotecan itself. Only a small fraction of irinotecan and its metabolites is eliminated in urine and a higher proportion in the bile, with an enterohepatic cycle of SN-38 glucuronide and SN-38. Significant relationships have been established between the AUCs of both irinotecan and SN-38 and hematological and intestinal toxicities, suggesting a potential use for monitoring of this drug.

L5 ANSWER 5 OF 6 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998384700 EMBASE
TI Pharmacology of irinotecan.
AU Kuhn J.G.
CS Prof. J.G. Kuhn, Department of Medicine, Univ. of Texas Hlth. Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284-6220, United States
SO ONCOLOGY, (1998) 12/8 SUPPL. (39-42).
Refs: 16
ISSN: 0890-9091 CODEN: OCLGE
CY United States
DT Journal; Conference Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Irinotecan (CPT-11 [Camptosar]), a semisynthetic derivative of the plant alkaloid camptothecin, is bioactivated by carboxylesterases (EC3.1.1-) to the topoisomerase I inhibitor SN-38, a minor metabolite. Bioactivation of intravenously administered irinotecan by carboxylesterases occurs predominantly in the liver. Two human ***carboxylesterase*** isoforms responsible for SN-38 formation have been characterized. At relevant hepatic irinotecan concentrations up to 12 .mu.g/mL, a low-Km isoform is responsible for irinotecan bioactivation. High concentrations of drugs commonly coadministered with irinotecan do not inhibit ***carboxylesterase*** activity. Intestinal carboxylesterases can also generate SN-38, followed by subsequent oral absorption. A second major polar metabolite of irinotecan, aminopentanecarboxylic acid (***APC***), is the product of CYP3A4-mediated oxidation of the terminal piperidine ring. ***APC*** is 100-fold less active than SN-38 as a topoisomerase I inhibitor and is a relatively weak inhibitor of acetylcholinesterase. SN-38 is eliminated mainly through conjugation by hepatic uridine glucuronosylansferase (UGT*1.1), the same isoezyme responsible for glucuronidation of bilirubin. Grade 4 irinotecan-related toxicity (ie, neutropenia, diarrhea) has recently been reported in two patients with deficient UGT*1.1 activity. SN-38 glucuronide (SN-38G), which has only 1/100th the antitumor activity of SN-38, is actively secreted into the bile by a canalicular multispecific organic anion transporter. Deconjugation of SN-38G to SN-38 by beta-glucuronidase produced by the intestinal flora may contribute to enterohepatic recirculation of SN-38 and delayed intestinal toxicity.

L5 ANSWER 6 OF 6 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2
AN 96250515 EMBASE
DN 1996250515
TI Identification and properties of a major plasma metabolite of irinotecan (CPT-11) isolated from the plasma of patients.
AU Rivory L.P.; Riou J.-F.; Haaz M.-C.; Sable S.; Vuilhorgne M.; Commercon A.; Pond S.M.; Robert J.
CS Department of Medicine, University of Queensland, Princess Alexandra Hospital, Ipswich Rd.,Woolloongabba, QLD 4102, Australia
SO Cancer Research, (1996) 56/16 (3689-3694).
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Irinotecan [7-ethyl-10-14-(1-piperidino)-1- piperidino]carbonyloxycamptothecin (CPT-11)] is a promising water-soluble analogue of camptothecin [S. Sawada et al., Chem. and Pharm. Bull. (Tokyo), 39: 1446-1454, 1991]. We have reported previously the presence of an important polar metabolite, in addition to 7-ethyl-10-hydroxycamptothecin (SN-381 .beta.-glucuronide, in samples of plasma taken from patients undergoing treatment with CPT-11 (L. P. Rivory and J. Robert, Cancer Chemother. Pharmacol. 36: 176-179, 1995; L. P. Rivory and J. Robert, J. Cromatogr., 661: 133-141, 1994). Plasma samples (0.5 ml) containing comparatively large amounts of this metabolite were extracted by solid-phase columns and subjected to high-performance liquid chromatography and mass spectrometry in parallel to fluorometric detection. The metabolite yielded [M+1] ions with a m/z of 619, representing the addition of 32 atomic mass units to CPT-11. Purified fractions were subjected to proton nuclear magnetic resonance, and the structure determined, 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]carbonyloxycamptothecin (***APC***), was further validated following synthesis. Like CPT-11, ***APC*** was found to be only a weak inhibitor of the cell growth of KB cells in culture (IC50, 2.1 versus

5.5 .mu.g/ml for CPT- 11 and 0.01 .mu.g/ml for SN-38, the active metabolite of CPT-11) and was a poor inducer of topoisomerase I DNA-cleavable complexes (100-fold less potent than SN-38). In contrast to CPT-11, ***APC*** was not hydrolyzed to SN-38 by human liver microsomes or purified human liver ***carboxylesterase*** . Furthermore, ***APC*** did not inhibit the hydrolysis of CPT-11 in these preparations. Interestingly, ***APC*** was only a weak inhibitor of acetylcholinesterase in comparison to CPT-11 and neostigmine. It appears likely, therefore, that ***APC*** does not contribute directly to the activity and toxicity profile of CPT-11 in vivo.

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